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SYNDROME CHARACTERIZED BY OSTEITIS FIBROSA DISSEMINATA, AREAS OF PIGMENTATION AND ENDOCRINE DYSFUNCTION, WITH PRECOCIOUS PUBERTY IN FEMALES*

Report of Five Cases

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IF pathologic manifestations, which at first seem to be totally disconnected, are found to occur together in a sufficient series of patients, some relation between them is apparent. Such is the case in the bizarre syndrome which is the subject of this paper. Five cases of this syndrome are reported here. A sixth case was seen at the Presbyterian Hospital in New York and is being reported in a separate communication by McCune.[1]† A seventh case was seen more recently in Albany and will be reported by Gorham, Campbell and Howard.[5]‡ In addition, in a search of the literature McCune and we ourselves have found 9 strikingly similar cases and 5 suggestively similar ones.

The characteristics of the syndrome are:

(a) Bone lesions which have a marked tendency to be unilateral and which show osteitis fibrosa on histologic examination.

(b) Brown nonelevated pigmented areas of the skin which tend to be on the same side as the bone lesions.

(c) An endocrine dysfunction which in females is associated with precocious puberty.

CASE REPORTS

Case 1. N. W. (M. G. H. No. 330635). The patient, aged 23, entered the hospital, July 9, 1933, complaining of pain in the right hip of 15 years' duration. Her trouble first began at the age of 8 when she sustained a fracture of the right femur while running about at play. She had had seven subsequent fractures of the right femur at different sites. There had been one fracture of the left humerus. All the fractures occurred without marked trauma.

The history of the catamenia was of interest in that her menstrual periods began at 7 and were established by the time she was 9. Secondary sexual characteristics began at 12. She was normal in size as a child, but stopped growing early. She had had brown spots on her skin since birth.

The rest of her past history and family history were not related to the present illness.

Physical examination showed a well-developed, small woman. Her height was 146 cm., her span was 157 cm. and she weighed 37.3 kg. The hair distribution was normal. There were several brown, nonelevated, pigmented areas in the skin over the coccyx and buttocks (fig. 1). The right femur was bowed anteriorly, and the right knee seemed partially dislocated. The right leg was 8 cm. shorter than the left. On the right leg two scars were evident, representing incisions from a former bone graft. There was anterior bowing of both humeri, and a small swelling was felt on the left lower rib anteriorly. The blood pressure was 115/80.

FIGURE 1. Pigment areas on buttocks in case 1. Note that lesions, except for one small spot, are confined to right side, as are most of the bone lesions (fig. 2).

The laboratory data were essentially normal. The

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†McCune's case was first reported in the Transactions of the Society for Pediatric Research, Annual Meeting, May 5, 1936.[2] Cases 1, 2, 3 and 4 in this publication were likewise reported in brief in the discussion of that paper. Cases 1 and 3 had previously been reported, before the condition was recognized as an entity.[3, 4]

‡Since this paper was prepared 2 additional cases in young men have been studied at the Massachusetts General Hospital.

red blood cell count was 5,900,000, and the white cell count 6,100. The hemoglobin was 85 per cent (Tallqvist), and the blood smear was normal. A serum Hinton test for syphilis was negative. The serum calcium determinations taken at various times were 9.4, 10.9 and 10.3, and the corresponding mg. per 100 cc. The examination of the urine showed nothing abnormal. No excess of follicle-stimulating hormone was found in the urine. Calcium and phosphorus metabolic studies showed values which were within normal limits (table 1).

The distribution of the bone lesions, as demonstrated by x-ray examination, is shown in figure 2. It will be noted that the lesions are predominantly right-sided, corresponding to the distribution of the pigmented areas of the skin. The roentgen appearance of the individual lesions (figs. 15, 16, 17) will be described below, together with the other 4 cases. The right ilium (fig. 15) was cystic throughout and was markedly smaller than the left, indicating that the disease interfered with growth.

A bone biopsy taken during the course of an orthopedic operation was reported as showing osteitis fibrosa cystica. A specimen taken from an uninvolved bone at the same operation showed no abnormality.

TABLE 1. *Calcium and phosphorus metabolic data on cases 1, 2 and 5.*

	Three Day Period	Calcium—gm. per day				Phosphorus—gm. per day				Serum—mg. per 100 cc.	
		Urine	Feces	Intake	Bal.	Urine	Feces	Intake	Bal.	Ca	P
Case 1.											
N. W.	I.	0.10	0.22	0.09	—0.23	0.39	0.10	0.46	—0.03		
(M. G. H. No. 330635)	II.	0.08	0.14	0.09	—0.13	0.34	0.20	0.45	—0.09	11.4	3.45
Case 2.											
O. R. G.	I.	0.10	0.44	0.10	—0.44	0.38	0.41	0.60	—0.19	9.3	3.1
(M. G. H. No. 353417)	II.	0.17	0.11	0.10	—0.18	0.67	0.13	0.60	—0.20	9.4	3.8
Case 5.											
L. R.	I.	0.06	0.12	0.10	—0.08	0.28	0.17	0.59	+0.14	9.9	4.0
(M. G. H. No. 358095)	II.	0.06	0.13	0.10	—0.09	0.41	0.17	0.59	+0.01	10.6	3.3
	III.	0.04	0.10	0.10	—0.04	0.43	0.15	0.59	+0.01		
Normal (6) Values		0.04	0.11	0.11	—0.04	0.40	0.20	0.69	+0.09	10.0	3.5

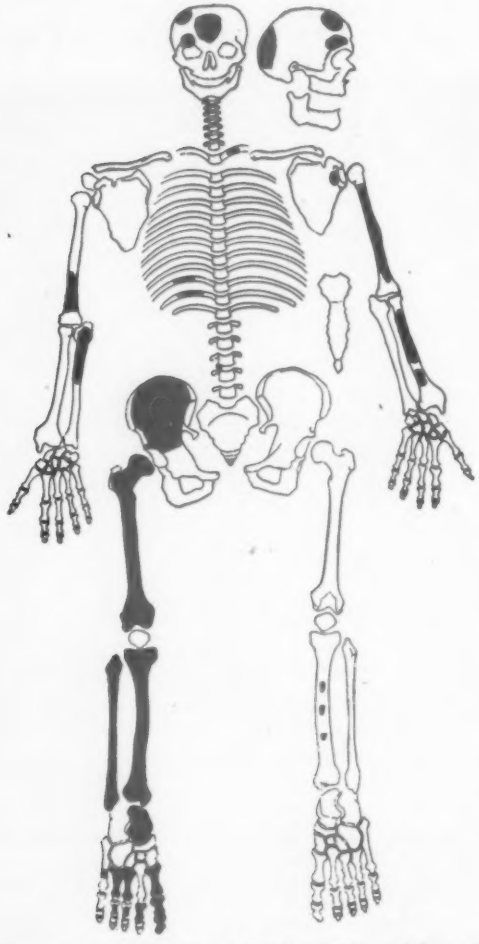

FIGURE 2. Diagram to show distribution of bone lesions in case 1. Note marked involvement of right leg with almost no involvement of left leg.

serum phosphorus determinations were 3.2, 2.5 and 3.4 mg. per 100 cc. Serum phosphatase determinations were 4.1, 3.9, 6.8 and 5.5 Bodansky units. Two serum cholesterol determinations were 229 and 155

Case 2. O. R. G. (B. M. No. 18632, M. G. H. No. 353417). The patient was referred to the hospital, at the age of 39, as a questionable case of hyperparathyroidism, by Dr. Paul P. Swett, of Hartford, Conn. She complained of intermittent pain in the region of the right hip of 29 years' duration. This pain followed a fracture of the right femur. The fracture was occasioned by a fall on the sidewalk while skipping rope when she was 10 years old.

Her catamenia began at 1 year of age and were very irregular at first. She was very large and mature for her age all through childhood, but stopped growing at 10 with the net result that she is quite small. From the age of 12 to 31 she had periods every 2 weeks. She was married at 24 and later became pregnant and was delivered of twins. Since her confinement her periods have been regular, occurring every 28 days. Recently her periods have been very profuse. She has had one succeeding pregnancy, but the child died. One of the twin boys has a small pigmented spot on his face, but x-ray examination shows no evidence of bone disease.

The physical examination was negative except for a marked convexity of the right femur, shortening of the right leg, and the remains of a patch of brownish pigmentation at the base of the neck, immediately to the right of the mid-line (fig. 3). The patch of pigmentation had originally been much larger, but the patient had had most of it removed by carbon-dioxide snow. She weighed 50.9 kg., her height was 150.5 cm. and her span was 152.2 cm. The distribution of fat and hair was normal. The blood pressure was 130/80.

The laboratory data were normal, with the possible exception of the serum calcium and inorganic phosphorus concentrations, which were slightly low.

The serum calcium was 8.8, 9.5 and 9.3 and the serum inorganic phosphorus 2.9, 2.4 and 3.1 mg. per 100 cc. The red blood cell count was 5,150,000, and the white count was 6,200. The blood smear was normal, and the hemoglobin was 75 per cent (Tallqvist). The urine was normal including the absence of Bence-Jones protein. The serum cholesterol was 139, 179 and 114 mg. per 100 cc. The serum phosphatase was 4.6, 5.0 and 3.3 Bodansky units per 100 cc. The serum protein was 6.9 gm. per 100 cc. A 24-hour specimen of urine, collected on the seventh day after a menstrual period, contained 21 rat units of estrin. One first morning specimen of urine was examined for an excess of the pituitary follicle-stimulating hormone, but no excess was found.

FIGURE 3. Remains of area of pigmentation on right side of back of neck in case 2. Remainder of pigment had been removed with carbon-dioxide snow. Note that pigment is on same side as bone lesions (fig. 4). Compare with figure 11.

Calcium and phosphorus metabolic studies were done. The data are shown in table 1. The values, when one makes certain allowances, are probably within normal limits. The high fecal calcium and phosphorus values in period I were probably attributable to constipation, in spite of the fact that she had been on the low calcium diet 4 days before collections were started. Since the patient was confined to bed because of a biopsy from the ilium, the slightly high urine calcium excretions were probably due to an increase in the calcium presenting for excretion because of bone atrophy of disuse. However, her catamenia began on the first day of period I and may have played a part in the marked differences between periods I and II (cf. especially the phosphorus excretion in the urine). In any case, the urinary calcium excretion in period I was too low to be consistent with even a mild degree of hyperparathyroidism.

Roentgenograms failed to demonstrate any abnormality of the pituitary or thymus glands. The distribution of the bone lesions, as demonstrated by roentgenograms, is shown in figure 4. The individual lesions (figs. 18, 19) will be discussed below. It will be noted that the bone lesions were confined to the right side, the same side as the pigmented spot.

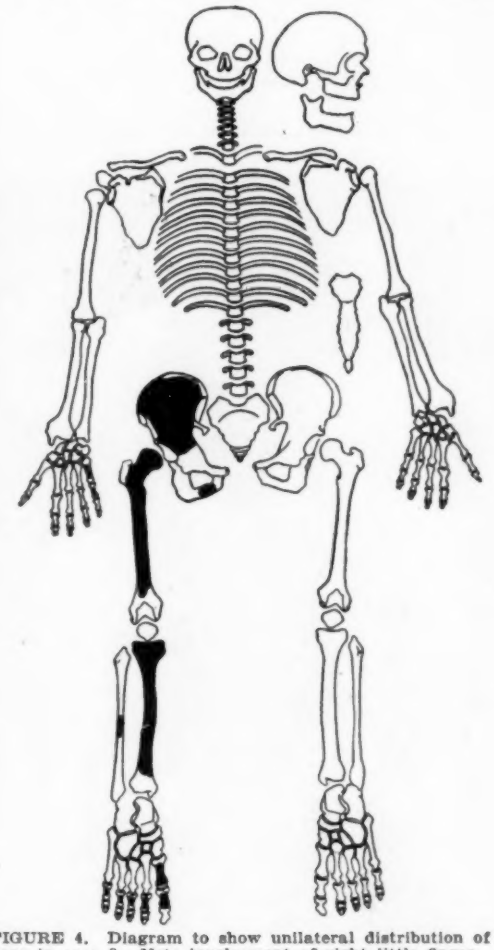

FIGURE 4. Diagram to show unilateral distribution of bone lesions in case 2. Note involvement of right little finger.

A biopsy taken from the crest of the right ilium showed scattered areas of what could be called osteitis fibrosa, in spite of the relatively few giant cells (osteoclasts) seen in the sections (fig. 13). No areas suggesting xanthomatosis were present.

Case 3. A. C. (C. H. No. A-177569) first entered the Children's Hospital at the age of 3½ years because of a fracture of the left femur incurred as the result of falling from a chair. This case had been reported previously as one of probable suprarenal disturbance.[3]

The patient was born in June, 1930, a full-term, 3.2 kg. baby, by a low-forceps delivery. There were no difficulty in initiating breathing, no hemorrhage, no convulsions and no paralyses. She was breast-fed for 1 month and then received a formula of milk, sugar and water. At the age of 2½ months she developed a fatty diarrhea and at that time weighed 3.6 kg. When she was 4½ months old, the stools

were noted to contain blood which from subsequent history was apparently of vaginal origin. At the age of 6 months she was taken to the Boston Dispensary, where she was found to be a small baby with a rachitic rosary, hypotonia, and hypertrophy of the clitoris and labia minora and majora. Brown pigmented areas of the skin were present at this time. A bloody, nonclotting vaginal discharge was found. The blood Wassermann and tuberculin tests were negative, as was also an Aschheim-Zondek test for pregnancy prolan. The uterus was not enlarged. The blood pressure was 90/55. During the following months, the pigmentation was said to have spread.

On entry, December, 1933, at 3½ years of age, she

FIGURE 5. Photograph of case 3 at the age of 3¾ years. Note extension of pigment down back of leg suggesting neurologic distribution. Note secondary sex development.

was an irritable, mentally retarded, sexually precocious girl. Areas of pigmentation, which had been noted before 6 months of age, were still present on the skin of the face, upper back, left buttock and posterior aspect of the left leg. Her appearance was approximately as depicted in the photograph (fig. 5) taken in April, 1934.

With the exception of a plasma phosphatase of 1.5 Kay units per 100 cc. (approximately 4 times normal), the laboratory data were within normal limits. Her blood pressure was 100/70. The red cell count was 5,300,000, the hemoglobin 80 per cent, and the white cell count 9,800, while the differential count was normal. A glucose tolerance test gave a normal curve. The urine had a specific gravity of 1.028 with no albumin and no sugar. The urinary sediment was normal. The serum calcium was 9.7 and the serum inorganic phosphorus 4.1 mg. per 100 cc.; the plasma cholesterol, 114 mg. per 110 cc.; the serum sodium, 133 and the serum chloride, 100 milliequivalents per liter. The urine contained no follicle-stimulating hormone or estrin by biologic assay. Intravenous pyelography showed normal renal pelves, calices and ureters and a good concentration of the dye in the urine.

X-ray examination showed widespread bilateral bone lesions (fig. 6). The individual lesions (figs.

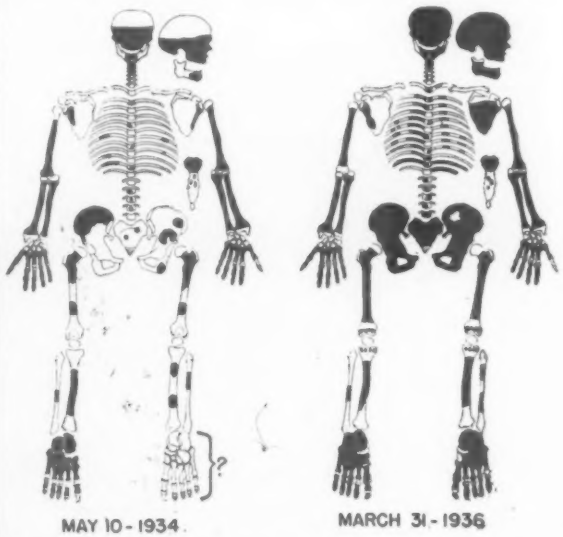

FIGURE 6. Diagram to show distribution of bone lesions in case 3 and progression of lesions since May, 1934. Note that almost entire skeleton is involved; compare with extensive distribution of pigment (fig. 5).

20, 21, 22, 23, 24) will be discussed below, together with those of the other patients of this group. There was an oblique fracture through the left femur about 2 cm. below the greater trochanter. The development of centers of ossification corresponded to that of a child of 7 or 8 years. Ventriculoencephalograms showed somewhat enlarged lateral and third ventricles with a moderate amount of air over the cortex, which findings were indicative of moderate cerebral deficiency.

In March, 1934, an exploratory operation of the adrenals was done, but no adrenal tumor was found. A small cyst adjacent to the left ovary was removed, which on microscopic examination was said to have originated from the embryonic mesonephros. The child was given six roentgen irradiations of the pituitary region in March, April and May, 1934. In December, 1934, she fractured the right femur.

She was seen again at 5¾ years of age at the Children's Hospital, in March, 1936. Since the last admission she was reported to have had regular menstrual periods every 3 weeks, using three pads a day for 3 days. Two months previous to her readmission, however, she had flowed for 3 weeks steadily. Physical examination showed a sexually overdeveloped, mentally retarded child, who walked with a waddling gait. Her hearing was not defective, but she talked little, and only a few of her words could be understood. The precocious sexual development was marked. Again the laboratory data, with the exception of an elevated plasma phosphatase of 0.9 Kay units per 100 cc., were normal. The serum calcium was 9.7 and the inorganic phosphorus 3.3 mg. per 100 cc.; the plasma cholesterol, 81 mg. per 100 cc.; the serum protein, 7.1 gm. per 100 cc.; the nonprotein nitrogen, 20 mg. per 100 cc.; and the urea clearance, 116 per cent of normal. There was no excess of follicle-stimulating hormone in the urine. This test was repeated four more times in December, 1936, with the same result. Four separate 24-hour specimens were ana-

lyzed for estrin, but none was found. The red blood cell count was 4,600,000, and the white cell count was 9,000, while the hemoglobin was 80 per cent. The blood smear was normal. There was a trace of Bence-Jones protein in one of three urine samples examined.

FIGURE 7. Case 4. Note area of pigmentation is on same side as most of skeletal lesions (fig. 8). A—location of bone lesion in skull.

X-ray examination at this admission showed marked progression of the lesions (fig. 6).

In September, 1936, the patient again entered the Children's Hospital for a skin and bone biopsy. Examination revealed little change since her previous admission. The skin biopsy was taken from the lateral aspect of the left thigh, just below the greater trocnanter. The incision was carried down to the bone, and a window of cortex and adjacent and deeper medullary material was removed.

The report of the microscopic findings (fig. 14) by Dr. Sidney Farber was as follows:

"The epidermis is of average thickness, and there is a thin, superficial layer of keratinized cells. The deeper granulosa cells contain a moderate amount of amber-colored pigment, and the stratum germinativum cells contain an abundance of similar pigment. Only an occasional pigmented macrophage is present in the superficial corium. The pigment does not stain with the iron stain so is apparently melanin. The connective tissue of the corium appears normal. An average number of hair follicles, sebaceous glands and sweat glands are present. The erector pili muscles are strikingly well-developed but otherwise not abnormal. The stratum reticularis, subcutaneous fat and fascia appear normal. The blood vessels and nerves are not remarkable. The skin findings are negative except for the deposition of melanin.

"The cortex of the bone is made up of irregular trabeculae and small irregular marrow spaces, which are filled with a young proliferating connective tissue. The margins of the bone trabeculae are being absorbed by large numbers of giant cells. Between the large trabeculae and the periosteum are numerous small trabeculae, some of which appear to be the remains of the superficial cortex, but most of them appear to be poorly formed, new trabeculae, as they are covered by osteoblasts and newly formed cartilage. The cortex is thin; and, below the thin layer of superficial trabeculae just described, the bone trabeculae are almost completely absorbed. Large masses of cartilage are present in this area, and a variable amount of osteoid tissue is present along the cartilage margins. Osteoblasts are present in large numbers along the surfaces of these masses of cartilage and osteoid tissue matrix.

"The connective tissue varies in type. That about the thin, irregular, newly formed trabeculae is more of the adult variety with abundant collagen matrix. This is exemplified in the subcortical area. Only occasional giant cells are present here, and the trabeculae are covered by a layer of osteoblasts, which are actively forming osteoid matrix. The connective tissue cells in the areas of absorption are of the young variety with large nuclei and a pale fibrillar matrix, which is scanty in collagen. Here, there are numerous giant cells, many of which are extremely large. Small cystic spaces and small hemorrhagic areas are seen, as a rule about the areas of absorption. The cysts apparently are degenerative lesions and usually begin near the large giant cells and in the areas of hemorrhage. The larger cysts are empty and are lined by a smooth layer of flattened, con-

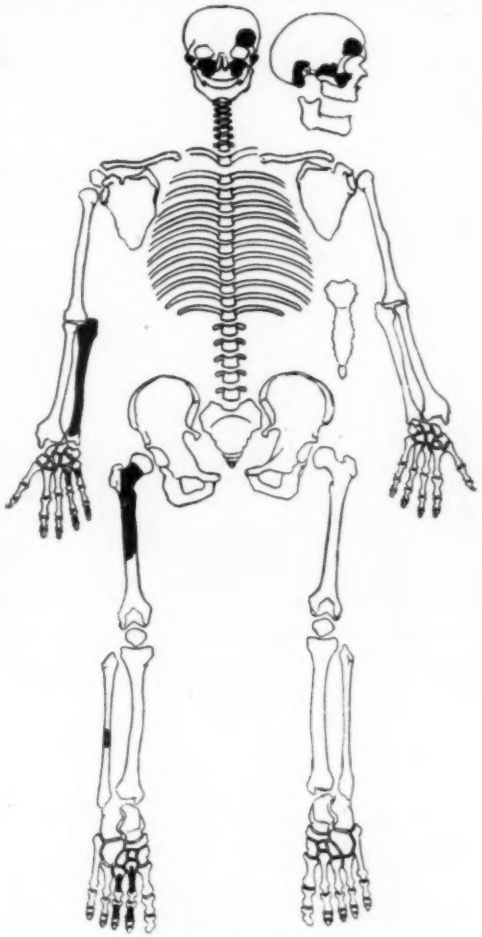

FIGURE 8. Diagram to show distribution of bone lesions in case 4. Note unilateral involvement except for skull lesions.

nective tissue cells. The connective tissue filling the marrow spaces is moderately vascular, but practically all of the vessels are of the small, poorly formed, capillary type. An occasional area is encountered where the newly formed connective tissue is diffusely infiltrated by red blood cells. Here, there are numerous giant cells, and occasional clumps of amber-colored pigment are scattered through this tissue.

"The material from the medullary area is similar to that previously described in the cortical area, except that bone formation is more prominent than bone absorption. There are numerous, irregular trabeculae of bone surrounded by osteoid matrix. The small, irregular marrow spaces are filled with a

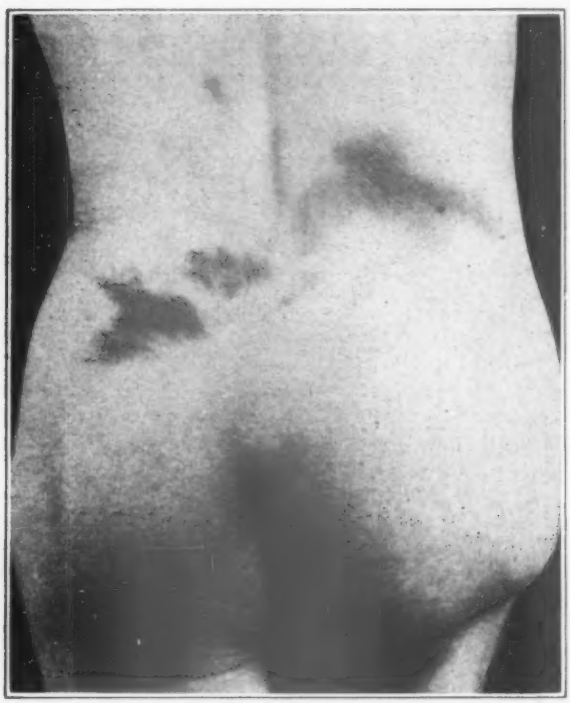

FIGURE 9. Areas of pigmentation in lumbar region in case 5.

connective tissue which has, for the most part, a moderate amount of collagen matrix. Osteoblasts are lined up along the bone trabeculae and are actively laying down osteoid matrix. Giant cells and cystic areas are present, but they are less numerous than in the cortical area. Numerous large deposits of pigment are encountered, and these are especially prominent about some of the larger cystic areas. Small masses of cartilage are found, and most of these are covered with osteoid matrix.

"The pathological findings are consistent with the diagnosis of osteitis fibrosa cystica."

Case 4. M. M., a patient of Dr. W. L. Crawford, of Rockford, Illinois, 8 years of age.* The patient's first catamenia occurred at 3½ years of age. Since then she has had periods every 3 to 4 months. On examination she showed early development of secondary sex characteristics. There were two pigmented areas, one over her right eye (fig. 7) and one over the lumbar vertebrae. There was a slight prominence of the frontal bone over the left eye (fig. 7, A).

The distribution of the bone lesions is shown in figure 8. The individual lesions (figs. 25, 26) will be discussed below.

A biopsy was made from the lesion in the left frontal bone. The report by Dr. Harold D. Palmer, of Rockford, Illinois, was as follows: "*Gross description.* The specimen consists of some curettements from bone. There is one shell-like piece of cortical bone about 1 cm. square and less than 1 mm. in thickness. The rest of the specimen is cancellous bone; in fact, it can hardly be described as cancellous bone, since it is made up more of soft tissue than bone. The soft tissue is tough, pink, and elastic in character. Throughout this are seen fine spicules of bone. Smears of this tissue which were warmed and examined for cholesterol crystals are negative. Some

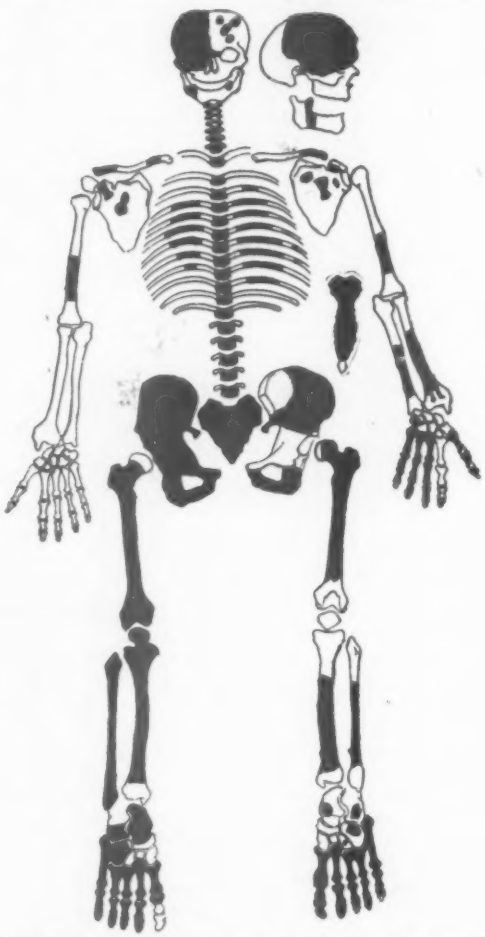

FIGURE 10. Diagram to show distribution of bone lesions in case 5. Note complete freedom of involvement of index finger of left hand. Spine was definitely involved.

of the tissue was extracted with ether, but no cholesterol is demonstrable in the extract. Some of the material was cultured aerobically and anaerobically. All cultures have remained sterile (7 days). *Microscopic description:* The sections present a tissue made up almost entirely of fibroblasts and intercellular substance. There is a very large amount of intercellular substance as compared to cells. The cells are adult fibroblasts. The intercellular substance is collagen and, in places, hyaline material—apparently bone matrix. There are widely separated, fine spicules of old bone. No giant cells are seen. There are no areas which contain foam cells. The whole structure microscopically is typical of osteitis fibrosa. *Diagnosis:* Osteitis fibrosa."

*This patient has not been seen by the authors, but there is no doubt that she belongs to the group, and Dr. Crawford has been kind enough to allow us to include her in this publication.

The laboratory data were normal. The serum calcium was reported as 11.5 and the serum phosphorus as 3.2 mg. per 100 cc., and the serum phosphatase as 2.1 Bodansky units.

Case 5. L. R. (M. G. H. No. 358095). This boy was first seen by one of us (F. A.) in June, 1932, at the Children's Hospital in Buffalo, at the request of Dr. A. Wilmot Jacobsen. At that time he was 10 years old. The patient had just undergone two parathyroid explorations in the belief that he was suffering from hyperparathyroidism. Two normal parathyroid glands had been removed. The development of some symptoms of tetany following the operation indicated that a parathyroid tumor had not been missed.

The patient was born at term after normal delivery on June 6, 1922. A limp was first noticed at the age of 4. Two years later, he slipped on the ice and fractured his right femur. The fracture healed without complications. He again fractured his right femur when walking behind a plow at the age of 8 years. At this time he was treated at the Strong Memorial Hospital in Rochester, New York. A diagnosis of osteitis fibrosa cystica was made. An osteotomy on the right femur was performed in July, 1930, in an attempt to overcome the deformity. He also received deep x-ray therapy over the leg. Another spontaneous fracture of the right femur occurred in June, 1932, and he was sent to the Children's Hospital in Buffalo.

The laboratory data, while he was at the Strong Memorial Hospital in Rochester in 1930, showed a serum calcium of 10.0 and a serum inorganic phosphorus of 4.1 mg. per 100 cc. Essentially normal values were also obtained from the serum calcium and the inorganic phosphorus levels at the Children's Hospital in 1932. The roentgen studies showed multiple bone lesions. These will be discussed below.

An osteotomy on the right femur was performed in January, 1933. A piece of bone tissue was examined by Dr. Kornel L. Terplan. It showed "very marked fibrosis of the bone marrow, with resorption and new formation of bone tissue." There were "no giant cells, as are often seen in typical osteitis fibrosa." It was Dr. Terplan's opinion that "all the changes may well represent one type of osteitis fibrosa, apparently of rather slow progress in the examined material.

The boy was discharged from the Children's Hospital in December, 1933. In the fall of 1935 he had another spontaneous fracture of the right femur and came under the care of Dr. Frederick D. Carr of Batavia, N. Y. Dr. Carr very kindly arranged to have him sent to Boston for study.

On physical examination in December, 1936, at the age of 14, he was a well-developed boy with marked deformity of his right leg, which was 7.5 centimeters shorter than his left. The right femur was markedly bowed. The skull was very irregular with protruding bosses, especially over the occipital region. Secondary sex characteristics were normal. Puberty had occurred at 12. The prostate felt normal, and the testes were definitely small. There were several areas of brownish pigmentation of the skin—several spots in the lumbar region (fig. 9), a small spot on the right side of the forehead, a spot on the left elbow and a small spot on the back of the right hand. The examination was otherwise noncontributory. A complete neurologic examination was negative.

With the exception of an elevated serum phosphatase and a flat sugar tolerance curve, the laboratory data were within normal limits. The serum phosphatase was 25.2 and 15.2 Bodansky units. A sugar tolerance curve, using 100 gm. of glucose by mouth, showed the following values: fasting, 102 mg.; after ½ hour, 108 mg.; after 1 hour, 108 mg.; after 2 hours, 116 mg.; after 3 hours, 89 mg. The serum calcium was 9.9 and 10.6 and the serum inorganic phosphorus, 4.0 and 3.3 mg. per 100 cc.; the serum protein, 7.0 gm. per 100 cc.; the serum nonprotein nitrogen, 15 mg. per 100 cc.; the serum cholesterol, 187 mg. per 100 cc. A renal function test with phenolsulphonphthalein showed excellent function. The urine examination and the hematologic studies showed nothing of note. No excess of follicle-stimulating hormone in the urine was found on four examinations. Three 24-hour urine specimens were quantitated for estrin with the following results: 25 rat units, 25 rat units, 38 rat units per liter.

Calcium and phosphorus balance studies were done while the patient was on a low-calcium, neutral-ash diet. These values were within normal limits (table 1).

The distribution of the skeletal lesions is shown in figure 10. The individual lesions (figs. 27, 28, 29, 30) will be discussed below. Careful appraisal of the epiphyseal development showed a degree of closure ordinarily observed in subjects 2 or 3 years older than the patient.

INDIVIDUAL CASES REPORTED IN THE LITERATURE

It seems not unlikely that the following cases taken from the literature may be examples of the syndrome reported above. It is of interest how differently they have been classified. The diagnoses include neurofibromatosis, juvenile Paget's disease, xanthomatosis, osteodystrophia fibrosa and osteitis fibrosa generalisata.

Cases Occurring in Females

Weil,[7] 1922. The patient was a 9 year old girl. Menstruation had begun at 1 year. Her bone age and secondary sex development corresponded to a girl of 15. There was abnormal distribution of pigment. Her first fracture had occurred at 1½ years, and since that time she had had seven fractures.

Gaupp,[8] 1932. *Case 1.* The patient, a girl of 9, had her first bone symptoms at 2. Her catamenia began at 9. X-ray examination showed involvement of both femurs and also cysts in the upper extremities. There was a hand-sized area of pigmentation on the left buttock. Bone biopsy showed osteitis fibrosa. Calcium studies were normal. No parathyroid tumor was found at operation.

Stalmann,[9] 1933. The patient, aged 8, had her first catamenia at 9 months. Bone symptoms started at 5 years and involved both femurs; there were spontaneous fractures. Areas of pigmentation were present. X-ray examination showed what was interpreted as osteitis fibrosa.

Snapper and Parisel,[10] 1933. The patient, aged 10, had the onset of puberty and her first catamenia at 7. Bone symptoms started, likewise, at 7, and she had spontaneous fractures of both femurs. On the skin of the face and chest were several small brown nevi. Parathyroid operations failed to uncover any parathyroid tumor. Her blood cholesterol on one occasion was 322 mg. per cent; later values being 197, 181 and 194 mg. per cent. Two bone biopsies showed changes similar to those in osteitis fibrosa; a third biopsy, however, showed nests of foam cells containing cholesterol esters in areas otherwise typical of osteitis fibrosa, and the diagnosis of xanthomatosis was made. A recent communication from Dr. Snapper states that until the last 4 months the patient had done well, some of the bone lesions tending to disappear while others extended. Four months ago,

however, a large swelling appeared on the hip which was diagnosed as a sarcoma. The patient's condition has rapidly declined.

Goldhamer,[11] 1934. The patient was a 9 year old girl. Her catamenia started at 2 years. A tumor of the left lower jaw was observed at 3 years; at the same time, symptoms appeared in the left femur. She sustained a fracture of the left femur at 5 years. The patient was left-handed. Pigmented nevi were present (fig. 11), which were almost all confined to the left side. The left leg was about 3 cm. shorter than the right. The serum calcium was reported

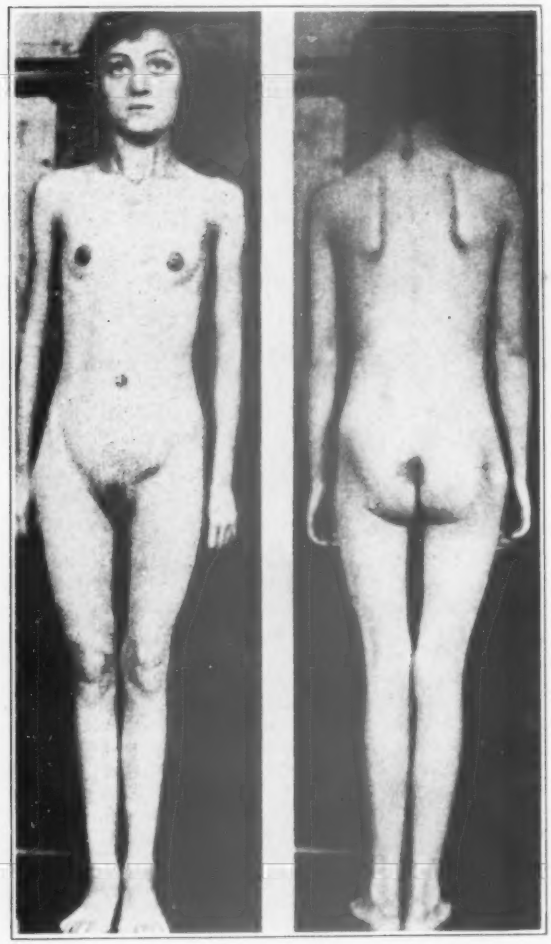

FIGURE 11. Reproduced from Goldhamer[11] by courtesy of *Fortschritte aus dem Gebiete der Röntgenstrahlen*. Girl of 9 with bone cysts confined to left side. Note precocity and confinement of pigmentation to left side. Compare distribution of pigmentation with that in cases 1 and 2 (figs. 1, 3).

as 11.4 and 12.0 and the serum inorganic phosphorus as 2.74 mg. per 100 cc. The blood cholesterol was 123 mg. per 100 cc. Roentgenograms showed bone lesions in the left upper and lower extremities, and in the left ischium. In the left hand and foot, the bone lesions decreased from the lateral aspect inward. The left side of the skull was also involved. A bone biopsy showed osteitis fibrosa without giant cells.

McCune,[2] 1936. The patient was a girl of 9 years. During the second year of life, irregular patches of dark-brown pigmentation had appeared in the skin, the patient had started to menstruate, and bone disease had become manifest. Sexual maturity had been completed at the age of 4, and hyperthyroidism developed at the same time. The basal metabolic rate was plus 65 per cent. The essential roentgen features were acceleration of maturation of the skeleton, thickening of the skull as in Paget's disease and cystic and productive changes throughout the whole skeleton, which, although bilateral, were more extensive and of greater severity on the right. Calcium and phosphorus metabolic studies were normal. The plasma phosphatase was elevated (23 to 37 Bodansky units). A bone biopsy was compatible with osteitis fibrosa cystica. No parathyroid tumor was found on exploration. It was suggested, in view of the negative evidence of hyperparathyroidism and the anomalies of pigmentation, that the skeletal lesions might be of the sort which have been reported in association with typical and atypical examples of von Recklinghausen's neurofibromatosis.

FIGURE 12. Reproduced from Hummel[12] by courtesy of *Röntgenpraxis*. Photographs demonstrate pigmentation in 2 cases reported by Hummel.

Cases Occurring in Males

Priesel and Wagner,[12] 1932. *Case 1.* A male, aged 13, developed pain in the right hip 2 years before admission. Examination showed a nevus, the size of the palm of the hand, in the region of the right side of the sacrum. There was no precocious sexual development. X-ray examination showed changes interpreted as osteitis fibrosa in the right femur, right ilium, right humerus, right fibula and both tibiae. No parathyroid tumor was found at operation. *Case 2.* A male, aged 6¾ years, developed pain in both femurs, 3 weeks before admission. Examination showed several pigmented nevi on his face, a nevus on his neck, which extended above his left ear, and another nevus on his back. X-ray examination showed evidence of osteitis fibrosa in the left femur, the bones of the left forearm, the right ulna and both humeri. No sexual precocity was noted.

Hummel,[12] 1934. *Case 1.* A male, aged 11, developed bilateral pigmentation (fig. 12) at the age of 1. Bilateral bending of both legs began at 7, and he sustained a spontaneous fracture of the left femur. A

biopsy of the bone at this time was interpreted as showing the mosaic structure of Paget's disease. The published photomicrograph throws doubt on this interpretation, however. At the age of 8 he broke the right femur. X-ray examination showed bilateral lesions similar to those in the other cases reported in this paper. There was no sexual precocity. *Case 2.* A male, aged 9½, developed pain in the left hip at 7½ years. The left leg became shorter, and an operation to correct a coxa vara was performed. Two years later, pain in the left lower leg began. There were bilateral areas of pigmentation on the back (fig. 12), and x-ray examination showed bilateral bone lesions, though predominately right-sided. There was no sexual precocity.

Cases in Which One or More of Characteristics of Syndrome Were Not Noted

Gaupp,[8] 1932. *Case 2.* The patient, a girl of 8, had her first catamenia at 3. Bone symptoms started at 2 and involved both legs. She underwent frequent spontaneous fractures. X-ray examination showed changes consistent with those of osteitis fibrosa, which were confined mostly to both femurs. There were also some small cysts in the metacarpals. The serum calcium concentration and calcium excretion in the urine were normal. Bone biopsy showed osteitis fibrosa with notably few osteoclasts. No parathyroid tumor was found at operation.

Salzer, quoted by Priesel and Wagner,[12] 1932. No information is given except that a girl with precocious puberty had, in addition, the classical signs of osteitis fibrosa cystica generalisata.

Freund,[14] 1934, and Freund and Meffert,[15] 1936. These authors reported the cases of 3 female patients with multiple, unilateral bone lesions, which by roentgenograms were similar to the lesions in our cases and which at biopsy examination were characterized as osteitis fibrosa. The condition was described as osteodystrophia fibrosa unilateralis and was differentiated from melorheostosis and Ollier's dyschondroplasia. The patients were 13, 22 and 23 years old and had had symptoms of bone disease since, respectively, 5, 4 and 8 years of age. Serum calcium and phosphorus concentrations were normal in all 3 patients. The parathyroid glands were explored in one case, and no adenoma was found. In a second case x-ray treatment of the parathyroid region was without benefit. No mention is made of cutaneous pigmentation or precocious sexual development.

Gorham, Campbell and Howard.[5] This patient had bone lesions and cutaneous pigmentation but no markedly precocious puberty. However, she was of Nordic stock and, whereas her mother's and sister's periods began at 18 years of age, her periods began at 14.

ROENTGEN APPEARANCE OF BONES

The entire skeleton of each of our patients has been examined by roentgenograms. Though such examination has revealed a variety of bone lesions rather than any specific one, x-ray examination of the complete skeleton of any one patient has been sufficiently characteristic to suggest the diagnosis.

The skeletal abnormalities are spotty in distribution and consist of multiple localized lesions, with normal bones elsewhere. In this respect this disease is similar to Paget's disease and xanthomatosis, and is different from hyperparathyroidism and osteomalacia. The lesions in many cases show a tendency to be unilateral; in almost all they are at least regional in that they tend to group themselves, for example, in one digit, or in one entire extremity (figs. 2, 4, 8, 10). When the skull is involved, there is less tendency to unilateral involvement.

There is no generalized decalcification as is seen in hyperparathyroidism. It will be recalled, furthermore, that in case 1, a biopsy from an affected portion of bone showed osteitis fibrosa cystica, while a section from one of the bones which showed no roentgenographic evidence of disease showed no histologic abnormality. This lack of involvement of all the bone tissue, as was emphasized when case 1 was first reported,[4] should make one immediately suspicious that the bone lesions are not directly due to metabolic or hormonal influences.

One of the most frequently seen individual lesions is an area of rarefaction, simulating a cyst (figs. 15, 25). For convenience such lesions will henceforth be referred to as cysts, although it must be remembered that it is almost impossible to differentiate by x-ray a bone cyst filled with fluid and an area of bone destruction filled with fibrous tissue. These cysts vary markedly in size, shape and density. They may be present in both the medulla and cortex of the long and flat bones (figs. 20, 23). Some may be sharply defined with very definite margins, while the majority of them fade out gradually into normal bone. Pathologic fractures frequently occur through the cysts. They usually heal well (fig. 18).

Areas of increased density, circumscribed and either homogeneous or granular, are frequently found (figs. 22, 28, 30, 31). These areas of increased density at times may lie in the cysts themselves (fig. 19). In some instances the increased density is apparently the result of an increased laying down of bone by the endosteum (fig. 28). This process may lead to almost complete obliteration of the medullary canal. The areas of increased density are very similar to those seen in the end stage of hyperparathyroidism some time after the removal of the parathyroid tumor (fig. 31). The involved bones may be markedly expanded (figs. 16, 17, 21). The cortex in these areas is very thin but intact in the absence of fracture (see below). The expanded medullary canal may present varying degrees of density. It may be filled with cystic areas or may present a homogeneous, opalescent increase or decrease in density (fig. 19). Still other areas show alternating vertical bands of increased and decreased density (fig. 22). These areas are not similar in appearance or distribution to those of alternating density seen in osteopoikilosis. In some areas in the medullary canals or in the flat bones, there are linear and

triangular areas of diminished density simulating "torn paper" (fig. 30). The bone trabeculae in the involved areas are absent.

Periosteal changes have occurred but rarely, except at the sites of fractures. Case 3, at the age of 3, showed diffuse subperiosteal, new bone formation along the shaft of the right femur. This hyperostosis produced a diffuse widening of the lower half of the femur and was more like that described by Freund and Meffert[15] than like melorheostosis. The punched-out areas shown in figure 22 were also observed. Similar lesions were not seen in the other cases.

The epiphyses often escape involvement when the entire remainder of the shaft is involved. In case 3, the epiphyseal lines were irregular. This was apparently due to the projection of islands of cartilage into the diaphysis of the bone (figs. 21, 23). It should be recalled that the bone biopsies in case 3 and in McCune's case showed islands of cartilage in the metaphyseal and diaphyseal portions of bone (see above). In those instances where the metaphyses in juxtaposition to the epiphyseal cartilages were involved, one cannot help getting the impression that the abnormal bone is the result of a dyschondroplasia of that particular epiphyseal cartilage (figs. 21, 22, 23). The finding of islands of cartilage in the bone strengthens this point of view. That an abnormal transformation of epiphyseal cartilage into bone cannot be the entire explanation of this condition is shown by the fact that lesions do occur in membranous bones. These observations are of interest as regards the possible relation of this syndrome to Ollier's unilateral dyschondroplasia (see below). In several of the involved bones in our cases, growth was retarded (fig. 15). However, one of the affected bones showed lengthening (fig. 19). Lengthening of bones was also noted in two of Freund and Meffert's cases.[15]

Precocious bone age and early union of the epiphyses are part of the syndrome. Thus, in case 3, at the age of 3 there were already eight carpal bones showing in the hand instead of three (fig. 21). The trochlea was likewise present, although it usually does not appear until 9. Her bone age, therefore, was 5 or 6 years advanced. Cases 1 and 2 were both short, but stated that they had been large as children and had stopped growing early. One can infer that they probably had early union of the epiphyses. Case 5, a boy with no evidence of precocious puberty, had a bone age about 3 years advanced.

In the skull, the bones most commonly involved were those in the base and the inferior portions of the orbital and frontal bones. The mastoid air cells and the accessory nasal sinuses may be completely obliterated by dense bone (fig. 20). The basisphenoid may be quite dense and thickened, even in the less advanced cases. In case 5 there was a local thickening of the frontal bone involving the roof of the orbit (fig. 27), not unlike that frequently seen proximal to a meningioma. In other cases the appearance of the skull due to the irregular calcium deposits within cysts might have suggested Paget's disease (fig. 17). In case 5, the local cysts in the parietal bones presented fairly distinct and sharp margins, giving an appearance not unlike that in xanthomatosis. In those cases where the bones of the face were involved and the sinuses were obliterated, one is reminded of leontiasis ossium (fig. 20).

The progressive character of the bone disease has varied greatly. Some cases have shown little change (case 2) and others have been rapidly progressive (case 3, fig. 6).

NATURE OF BONE LESIONS

Biopsies on 9 cases have been interpreted as osteitis fibrosa. Osteoclasts have been notably infrequent (cases 1, 2, 4 and 5 and those reported by Gaupp[8] and Goldhamer[11]). However, in case 3, which had progressing bone lesions, there were many osteoclasts (fig. 14). Inasmuch as there are areas of bone which are not affected, even on microscopic examination (case 1), the condition would have to be classified as osteitis fibrosa localisata as opposed to osteitis fibrosa generalisata. Because the lesions are multiple, however, the designation osteitis fibrosa disseminata has been used.

The absence of osteoclasts fits in with the fact that in most instances the condition is very slowly, if at all, progressive, and with the tendency for the bones to show areas of increased density by roentgen examination (see above). One is reminded of bone biopsies taken from patients several weeks after the removal of a parathyroid tumor. There one sees fibrosis and osteoblasts, but no osteoclasts.[19] Attention has already been called to the similarity between the roentgen appearance of the bones of healed hyperparathyroidism and certain of the lesions observed in our cases (fig. 31).

The points of difference have been discussed above. The serum calcium and inorganic phosphorus values are within normal limits, and the urinary calcium excretion is not elevated. These findings should dispel any remaining doubt as to the connection with hyperparathyroidism. The cases with very advanced bone changes do have elevated serum phosphatase levels (cases 3 and 5 and McCune's[2] case). Although no cases were explored for hyperparathyroidism at the Massachusetts General, Infants' or Children's hospitals, it is of interest that it is because of a mistaken diagnosis of hyperparathyroidism that most of these unusual cases are now coming to light. Thus cases 1

and 2 were referred to one of us (F. A.) with such a diagnosis. Case 5 had already been explored for hyperparathyroidism when first seen by one of us (F. A.). Six of the cases reported in the literature were operated upon without the finding of parathyroid disease.[2, 5, 8, 10, 14]

Though there is some similarity between this syndrome and that of neurofibromatosis, the evidence from the histologic examination of biopsy material from 11 of the 18 cases reviewed here did not prove the diagnosis of neurofibromatosis in a single case.

The finding of islands of cartilage in the biopsy specimens and the suggestion that these might have come from the epiphyseal cartilage bring up the possibility of a dyschondroplasia (see discussion under Ollier's disease below). This finding is not characteristic of the usual osteitis fibrosa localisata or generalisata.

Hummel[13] interpreted his 2 cases as having juvenile Paget's disease because the biopsies showed the mosaic structure characteristic of this disease. From one published photomicrograph, however, it seems doubtful if the true mosaic pattern of Paget's disease was present.

Snapper,[10] after a careful search, found in his case, besides areas of osteitis fibrosa, other areas of typical foam cells and considered the condition xanthomatosis. Similar areas have not been found on other patients, but the search for them should be continued. The possibility exists that the foam cells in Snapper's case did not represent true xanthomatosis, but were merely localized areas of cholesterol deposit, as is sometimes seen in osteitis fibrosa. The cholesterol studies on his patient were not very convincing of xanthomatosis, and those on others of this group have not shown noteworthy changes. The distribution of the lesions in many of the cases, furthermore, is not that of a metabolic disease. If the disease could be shown to be a disorder of lipoid metabolism, this might rationalize its connection with precocious puberty, as estrin is closely related chemically to cholesterol. Part of the biopsy specimen on case 2 was extracted for estrin but none was found.

PIGMENTATION

The pigmentation is one of the cardinal features of the disease. It is patchy, and the individual patches tend to remain on either one side or the other of the midline (figs. 1, 3, 5, 11, 12). They occur most frequently over the sacrum, buttocks and upper spine (cases 1, 3, 4 and 5, Goldhamer's[11] case, Priesel and Wagner's[12] case 1, and Hummel's[13] cases). The patches do not show much evidence of having the same distribution as cutaneous nerves. In case 3 (fig. 5), however, the patch did run down the back of the leg. McCune[2] has called attention to the similarity of this pigmentation with that seen in neurofibromatosis. Stalmann's[9] case was considered to be one of neurofibromatosis. The melanoblasts normally present in the stratum germinativum and abnormally abundant in the cutaneous pigmentation of neurofibromatosis are generally believed to be of ectodermal origin. The skin biopsy from case 3 showed the pigment to be melanin, present in the melanoblasts of the epidermis and corium. The diagnosis was melanin deposition in the skin.

The skin over the lower lumbar region and the buttocks is the most frequent site of pigmentation (cases 1, 3, 4 and 5, Goldhamer's[11] case, Priesel and Wagner's[12] case 1, Hummel's[13] cases and probably others). The back of the neck is another frequent site (case 2, Goldhamer's[11] case, Priesel and Wagner's[12] case 2). In case 3 a biopsy of the skin showed that the pigment was probably melanin. This distribution suggests a relation with the melanoblasts of mesodermal origin which occur in the corium over the sacrum and the back of all infants. It is such melanoblasts that cause the "blue spots", often seen in pigmented races.

The amount of pigmentation varies roughly with the degree of involvement of the skeleton (compare cases 1 and 2 with case 3 and McCune's[2] case). When the bone disease is unilateral or almost unilateral, the pigment tends to be unilateral, or almost so, and on the same side as the bone disease (cases 1, 2 and 4, Goldhamer's[11] case, Priesel and Wagner's[12] case 1). When the bone disease is bilateral, the pigment tends to be bilateral (cases 3 and 5, Hummel's[13] cases 1 and 2, McCune's[2] case).

DISTRIBUTION OF BONE AND SKIN LESIONS AND POSSIBILITIES AS TO THEIR ETIOLOGY

In some of the cases the pigmentation and bone lesions are confined to one side (case 2, Goldhamer's[11] case); in more cases the changes are predominantly on one side (cases 1 and 4 and McCune's[2] case); in a few cases the disease is apparently so extensive that neither side escapes (cases 3 and 5 and Hummel's[13] cases 1 and 2). This distribution of the cutaneous and bone lesions suggests an embryologic or neurologic disturbance. The former would be more likely if the pigmentation were due solely to melanoblasts of mesodermal origin. An embryologic defect in a sclerotome then could be associated with both the cutaneous and the bone lesions. Though the distribution of the pigmented areas is such as to suggest a mesodermal origin, the histologic evidence indicates that most of the melanoblasts are of ectodermal origin. This would seem to require an embryologic disturbance affecting both ectoderm and mesoderm.

The unilateral character of the syndrome is similar to that observed in Ollier's dyschondroplasia, where multiple enchondromas of the skel-

eton are confined to one side. Case 3 and McCune's[2] case, interestingly enough, showed islands of cartilage in the biopsy specimens. Case 3 by roentgen examination showed a definite tendency in places for the bone lesions to start from the epiphyseal cartilage (fig. 22). Furthermore, the tendency for the involved bones to be smaller (fig. 15) suggests a connection with Ollier's disease, as this is one of the characteristics of the latter condition. However, no case of Ollier's disease with precocious puberty or pigment spots was found;[16, 17, 18] and, as pointed out above, one could not explain lesions in membranous bones by a dyschondroplasia.

PRECOCIOUS PUBERTY

The disease in the female is attended by precocious puberty with early union of the epiphyses. In the male cases puberty apparently comes on at about the normal time with less marked, if any, precocity. However, since the time of puberty is less apt to be commented upon in the male, and since only 5 male cases, including our case 5, have been collected, this point is not definitely settled. Case 5 did have slightly precocious bone development. Moreover, the small testes suggested a disturbance in sex function, although the secondary sex development was normal.

The endocrine disturbance is very dissimilar to that seen with pineal, pituitary, basophilic or adrenal tumors. In case 3 an adrenal exploration was carried out, but nothing was found. A granulosal cell tumor of the ovary might cause a precocity of a similar nature in girls, but such tumors do not run a benign course, and no such tumor was found at operation in case 3. In some ways the precocity is more analogous to that seen in Rowntree's[20] rats, which were fed on thymus extract. These rats were both precocious and fertile, as were the female patients discussed above. But marked precocity in such rats occurred in both sexes, whereas precocity in the male patients under discussion is not definite.

One can make out a better case for a disturbance of the follicle-stimulating hormone of the anterior pituitary gland and, at the same time, possibly explain the different effects of the disease on the two sexes. The evidence for this assertion rests on certain facts presented in the following short summary of the present knowledge of the gonad-stimulating hormones of the pituitary.

In the first place, there is apparently no difference between these pituitary hormones in the two sexes. Thus, Greep[21] was able to transplant pituitary bodies from male donors into hypophysectomized female recipients and have the female recipients develop estrus cycles, become pregnant, bear young and lactate. Next, there are at least two gonad-stimulating pituitary hormones, follicle-stimulating hormone (F.S.H. = pituitary prolan A = Rho I) and luteinizing hormone (L.H. = pituitary prolan B = Rho II).* In the female, F.S.H. causes follicle ripening in the ovary and the production by the ovary of estrin. Estrin influences the secondary sex characteristics. L.H. causes corpus luteum formation and the production by the ovary of progestin. In the male, F.S.H. causes development of the tubules of the testis and spermatogenesis but it has not been demonstrated that it leads to the production of any hormone by the testis analogous to estrin.[23] L.H. (or at least the L.H. fraction) stimulates the interstitial cells of the testis and leads to the production of the male sex hormone, which, in turn, influences the secondary sex characteristics. Presumably puberty is initiated by the increased production, or liberation from the pituitary, of the gonad-stimulating hormones.

From the facts given above, it is clear that puberty in the female depends on the production of F.S.H., and in the male on the production of L.H. It is possible that girls reach puberty before boys because F.S.H. production starts before that of L.H. The hypothesis cannot help suggesting itself that in the disease under consideration there is a disturbance of the F.S.H. hormone. Early production of this hormone presumably would lead to secondary sex development in females. The fact that the only 2 patients in the series who became pregnant (case 2 and the case of Gorham et al.[5]) both had twins lends a little weight to the possibility of a F.S.H. disturbance, as an excess of this hormone causes multiple follicles to ripen in the ovary. The twins of case 2 were not identical; those of the patient described by Gorham et al.[5] had not been born at the time of writing.

In males no striking sexual precocity would be expected from an early production of F.S.H. Early development of the tubules of the testes and precocious spermatogenesis theoretically might result, but there is always the possibility that overstimulation might lead to exhaustion and tubular atrophy.† In case 5 the small

*Evans, Korpi, Simpson, Pencharz and Wonder[22] have recently produced evidence that there is a third gonad-stimulating hormone—the "interstitial cell-stimulating hormone" (I.C.S.H.). This, in the female, acts on the interstitial cells of the ovary and, in the male, on the interstitial cells of Leydig of the testicle. Their findings are perhaps compatible with those of Greep, Fevold and Hisaw,[23] here referred to, if one assumes that the L.H. of the latter contains I.C.S.H. as well. Whereas Greep et al. found that L.H. stimulated the Leydig cells and hence led to the production of the male sex hormone, Evans et al. believe this stimulation was due to the presence of I.C.S.H. in their L.H.

None of the hormones here referred to must be confused with the gonad-stimulating hormone of the urine of pregnant women (pregnancy prolan = P.U.).

†The testes were not definitely abnormal in either of 2 cases in young men studied since this report was written.

testes may have been due to such atrophy. The normal development of secondary sex characteristics and the normal size of the prostate indicated normal L.H. function.

In cases 1, 2, 3 and 5, F.S.H. was looked for in the urine on repeated occasions but no demonstrable increase was found. However, McCune[2] found some F.S.H. present in his case on several but not all occasions. These findings suggest that, if a disturbance of F.S.H. is present, it is more likely that this disturbance is an early production, or release, of the hormone rather than an overproduction.

From the work of Smith[24] it is known that the gonad-stimulating hormones are present in the anterior pituitary long before puberty, in fact before birth. Therefore, the onset of puberty is not due to the onset of the production of these hormones. Some other mechanism must come into play, possibly a releasing mechanism. It may be this other mechanism which is disturbed in the disease under consideration.

There is some evidence that this mechanism may be connected with nerve impulses. The fact that the rabbit usually ovulates only after copulation suggests a nerve mechanism for the release of pituitary hormones. Friedgood[25] was able to cause ovulation in rabbits by stimulation of the cervical sympathetic nerves, which fact suggests that the impulses travel over the sympathetic system. Brooks,[26] on the other hand, found that copulation still led to ovulation in rabbits that had had both sympathetic chains completely removed. He further found[27] that rabbits with their pituitary stalks interrupted failed to ovulate following coitus, which suggested that efferent nerve impulses may reach the pituitary gland by this route.

RELATION OF ENDOCRINE DISTURBANCE TO OTHER MANIFESTATIONS

It might be wiser only to describe the condition and not to try to come to any conclusion concerning its etiology and the relation of one manifestation to another. Certain observations seem warranted, however. As has been discussed above, the distribution of the bone lesions and of the pigment spots is consistent with some embryologic disturbance or with some trophic neurologic disturbance. This distribution certainly makes an endocrine cause for the condition seem unlikely, as a hormonal influence should not affect one leg only and should not stop in the midline. The fact that there was underdevelopment of the affected side of the face in Freund's[14] case could fit either an embryologic or a neurologic hypothesis. The sex disturbances are undoubtedly hormonal, although they may be initiated by nervous influences (see above). It is easier to believe that a hypothetical neurologic disturbance, which causes the bone and pigment changes, likewise initiates the endocrine disturbance, than to assume that an endocrine disturbance causes the bone and pigment changes. Perhaps the fact that the patient in case 3, the most severely affected individual in the series, is mentally very defective adds weight to the theory that the condition is due to some widespread disorder of nervous tissue. On the other hand, it is possible that the whole syndrome represents some embryologic defect affecting multiple systems.

FREQUENCY, PROGNOSIS AND TREATMENT

If this disease occurs only in its complete form, it must be rare. Certainly examples such as case 3 and McCune's[2] case are rare, for similar cases would have attracted enough attention to have been reported. But the last group of cases from the literature raises the question whether the disease may be present when only one or two of the triad of symptoms are noted. If the disease occurs in such incomplete forms, it may be less rare than is now apparent.

The prognosis for a case seen early in life would be difficult to give on the basis of information derived from the cases reported here. The age at which the symptoms were first noted seems to have but little relation to the progression of the disease (cases 2 and 3). Certainly, a prognosis of serious disability with recurrent fractures and deformities seems justified. The relation of this syndrome to mental development must await further observations.

There is obviously little to say about the treatment of this disease until more is known of its etiology. X-ray therapy was given over local bone lesions in cases 2 and 5 and in Snapper's[19] case, with questionably beneficial results. Radiation of the pituitary was tried in case 3 without demonstrable effect on the progress of the disease. Radiation of the parathyroid region without apparent benefit was tried in one of Freund and Meffert's[15] cases.

SUMMARY AND CONCLUSIONS

Attention is called to a syndrome characterized by:

(a) Multiple bone cysts which have a distribution suggesting a relation to nerve roots or to an embryologic defect in the myotomes.

(b) Areas of pigmentation which have a distribution suggesting some connection with the bone cysts.

(c) Precocious puberty in females but apparently not in males.

Four cases in females and 1 case in a male are reported, 13 cases are reviewed from the literature, and 1 unpublished case is cited.

The precocity is unusual in that it does not lead to sterility or to other endocrine disturbances. Certain circumstantial evidence, especially the fact that the precocity apparently does not occur in males, suggests the hypothesis that this part of the syndrome is due to a disturbance in the follicle-stimulating hormone of the anterior pituitary.

Small testes with normal secondary sex characteristics were present in the 1 case here reported occurring in a male.

The bone lesions consist of multiple circumscribed areas of what appears to be osteitis fibrosa with normal bone elsewhere. The term osteitis fibrosa disseminata is suggested to differentiate the condition from osteitis fibrosa generalisata (hyperparathyroidism) and osteitis fibrosa localisata (solitary bone cyst). Several of the cases observed elsewhere were confused with hyperparathyroidism. The bone manifestations, however, differ from hyperparathyroidism in that they are spotty rather than generalized and are not attended by changes in calcium and phosphorus metabolism.

The suggestion is made that the endocrine disturbance as well as the bone lesions and pigment spots may be manifestations of an underlying neurologic disturbance or of an embryologic defect.

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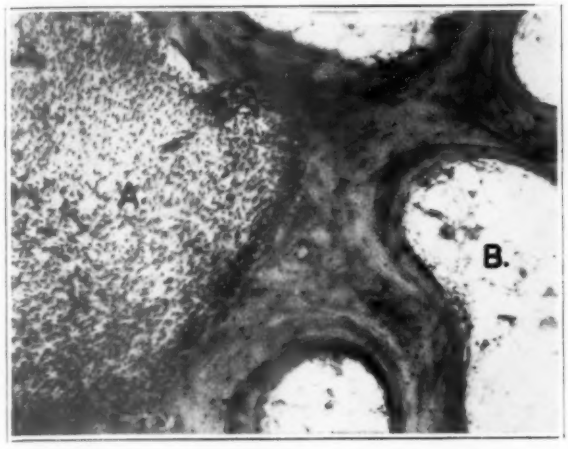
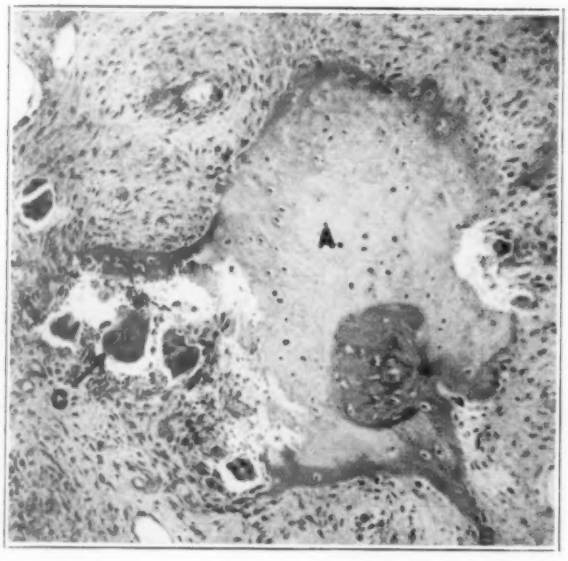


FIGURE 13. Photomicrograph of biopsy of ilium from case 2. Note circumscribed area of fibrosis (A) in juxtaposition to normal areas of fatty marrow (B). Note absence of osteoclasts.



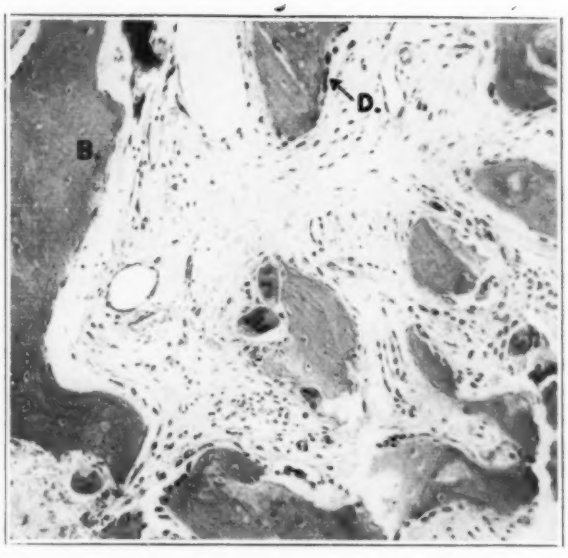


FIGURE 14. Photomicrographs of biopsy from case 3. A—area of cartilage; B—area of bone; C—osteoclast; D—row of osteoblasts. Authors are indebted to Dr. Granville Bennett of the Department of Pathology for the photomicrographs.

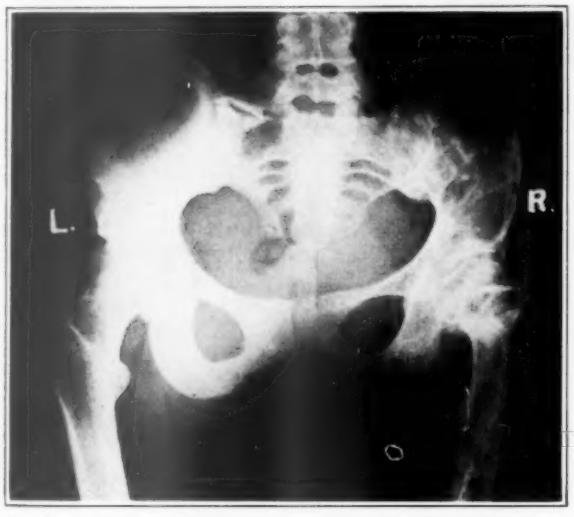


FIGURE 15. Case 1. X-ray of pelvis. Note striking unilateral aspect of disease. Note that involved side is smaller, indicating interference with growth. Individual lesions suggest cysts.

FIGURE 16. Case 1. X-ray to show cyst in right humerus and right twelfth rib. Note homogeneous character of cyst in humerus.

FIGURE 17. Case 1. X-ray of skull. Note marked tendency for involved bone to be expanded, in this respect resembling Paget's disease.

FIGURE 18. Case 2. Note healed fracture at A. Note also involvement of right ilium (B) with normal left ilium. Again, involved bones are smaller. (Compare fig. 15.)

FIGURE 19. Case 2. Note involvement of right tibia with normal left tibia. Note circumscribed area of increased density at upper end of right tibia. As suggested in illustration, the involved tibia was longer than the other.

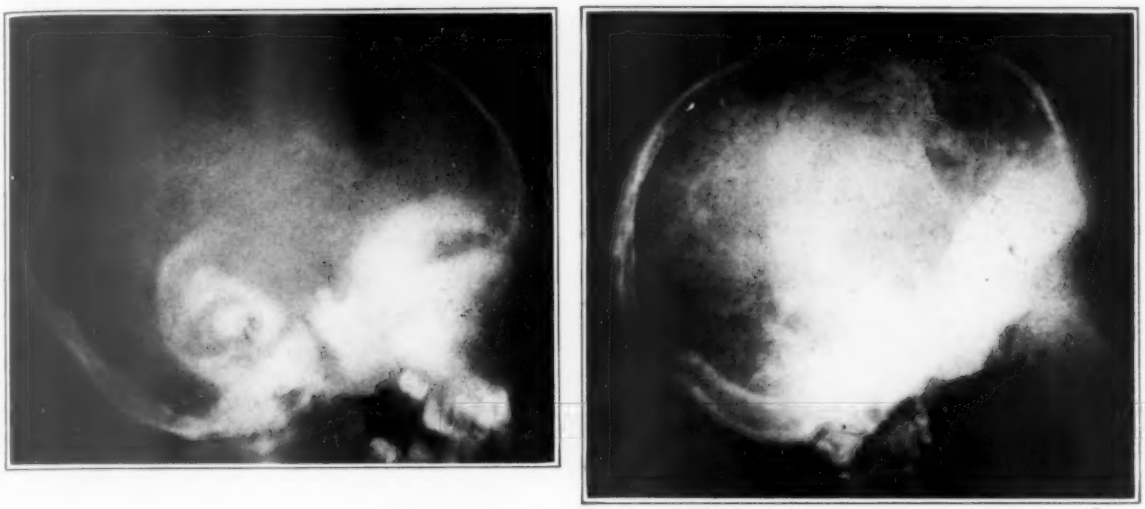


FIGURE 20. Case 3. X-rays of skull taken in December, 1933 (left), and in March, 1936 (right). Note marked progression of disease with cystic appearing areas over entire calvarium in later view. Note marked density of bones at base of skull.

FIGURE 21. Case 3. X-ray of hand taken in December, 1933, at age of 3½ years. Note advanced bone age with eight carpal bones showing (normal for age is three). Note involvement of all metacarpals and phalanges. Note that epiphyses appear least, if at all, involved. Carpal bones are also spared. Note increased thickness of involved bones.

FIGURE 22. Case 3. X-ray of bones of forearm, March, 1936. Note apparent island of cartilage extending from epiphyseal cartilage of ulna into diaphysis of bone. Note alternating linear areas of increased and decreased density at A. Note granular area of increased density at B, an appearance often seen at the end of a diaphysis.

FIGURE 23. Case 3. X-ray of pelvis, March, 1936.

FIGURE 24. Case 3. X-ray taken March, 1936. Note punched-out areas in shaft of ulna. This appearance was not seen in other cases.

FIGURE 25. Case 4. Note bone cyst in upper portion of right femur, with normal bones elsewhere.

FIGURE 26. Case 4. Note sharply circumscribed lesion in frontal bone.

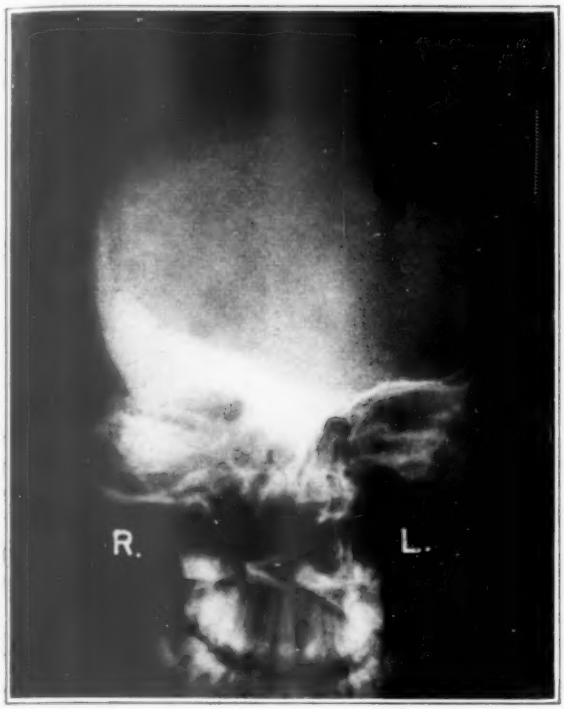


FIGURE 27. Case 5. X-ray of skull. Note area of increased density at base of skull in frontal region on right.

FIGURE 28. Case 5. Note marked thickening of cortex of right tibia due to endosteal proliferation. Process almost fills marrow canal at A. Note patchy linear areas of increased density in right femur.

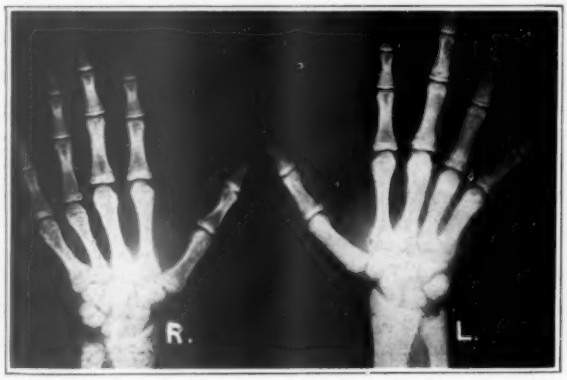


FIGURE 29. Case 5. X-ray of hands. Note complete absence of involvement of right hand and of index finger of left hand.

FIGURE 30. Case 5. X-ray of pelvis. Note "torn paper" effect in left ilium apparently due to line of division between area of increased density at A and normal bone at B. Note similar appearance at C.

FIGURE 31. A. X-ray of right foot of case 2. B. X-ray of hand of patient with hyperparathyroidism. C. X-ray of same hand as B, 4½ years after removal of parathyroid tumor. Note similarity between area of increased density in first phalanx of big toe (A) and that in second metacarpal (C). Compare also cyst in first phalanx of middle toe with cyst in third metacarpal (B and C). Note that when hyperparathyroidism heals, true cysts (third metacarpal) remain cysts, whereas cystic-appearing areas (second metacarpal) may organize into dense bones.

THE TREATMENT OF CARDIOVASCULAR EMERGENCIES*

BY JAMES M. FAULKNER, M.D.†

IN choosing the subject of this paper, I have had in mind the expressed desire of your president that it should be something of a practical nature concerning the heart. Since cardiovascular emergencies are common in the experience of almost every practitioner of medicine or surgery, I have chosen to speak of the accepted methods of treatment, a matter of broad practical interest. I shall lay particular stress on the recent developments in treatment.

DISTURBANCES OF RHYTHM

Auricular paroxysmal tachycardia. In the first place, let us consider what might be termed the minor cardiac emergencies or disturbances of rhythm. The most common of these is auricular paroxysmal tachycardia. It is characterized by the sudden onset of a very rapid, regular, cardiac rhythm with a rate of from 160 to 220. Its chief subjective manifestation is palpitation, which is frequently described as a fluttering sensation in the chest and which is often associated with faintness and vertigo, which compel the victim to lie down. Usually it lasts from a few seconds to a few minutes or, not uncommonly, for several hours. In some cases it may persist for days or weeks. In most cases it is not associated with heart disease and is important only for the reason that it causes annoying periods of discomfort and incapacitation. In the presence of underlying heart disease and in the rare cases where the rate is extremely rapid and persistent, congestive failure and even death may result.

The most satisfactory treatment of this condition is stimulation of the vagus nerve. This may be done in various ways, such as by direct pressure over one or both carotid sinuses, by pressure on the eyeballs or by touching the back of the throat so as to cause gagging. Such measures bring about abrupt cessation of the attack in more than half of the cases. In cases that do not respond to these simple procedures, more intense vagal stimulation in the form of an emetic is indicated. The most satisfactory emetic is ipecac, a drug that has not yet received due recognition in the treatment of paroxysmal tachycardia. In my experience, it has been successful in a number of cases where other drugs, including quinidine, have failed. Patients in whom the tachycardia persists in spite of emetic doses of ipecac should be digitalized promptly. Digitalis sensitizes the vagus endings, and thus makes vagal stimulation more effective.

The following case is an illustration of the effect of vagal stimulation in this condition.

L. L., a 20 year old man with active rheumatic heart disease, marked aortic regurgitation and mitral stenosis without signs of cardiac decompensation, developed an attack of auricular paroxysmal tachycardia with a rate of 180. He had already been well digitalized. The attack did not respond to pressure on the carotid sinus or eyeballs or to gagging. He was given 30 grains of quinidine in one day without relief. The next day he began to show signs of congestive failure at the lung bases, and he was given ipecac until he vomited; but still the tachycardia persisted. Then, while he was still vomiting, firm pressure was applied to both eyeballs, and the attack stopped abruptly and did not return.

Another method of producing vagal stimulation is by the injection of methyl-beta-acetyl cholin. This drug, in subcutaneous doses of 10 to 50 mg., has been proved to be successful in restoring normal rhythm in 90 per cent of the cases. Although its effect on the heart is also associated with less desirable reactions, such as sweating, nausea, vomiting and sometimes collapse, it appears to be a relatively safe drug. Both ipecac and methyl-beta-acetyl cholin are more effective than quinidine in the treatment of auricular paroxysmal tachycardia, and there is, moreover, an antagonistic action between the two drugs, so that vagus stimulation is distinctly less effective when quinidine has already been administered. It is, therefore, desirable to withhold quinidine until the possibilities of vagal stimulation have been exhausted. Quinidine may be given by mouth in doses of 6 grains every 2 hours for five doses. In desperate cases it may be given intravenously in doses of from 4 to 6 grains.

Ventricular paroxysmal tachycardia. A condition that closely simulates auricular paroxysmal tachycardia in its very rapid, regular heart rhythm is ventricular paroxysmal tachycardia. The latter condition is, however, usually associated with serious heart disease, particularly with coronary thrombosis. Not infrequently it is merely the momentary precursor of ventricular fibrillation and death. The diagnosis, which can be established with assurance only with an electrocardiogram, is not often made. The occurrence of runs of ventricular extrasystoles in twos or threes is a warning, however, that ventricular paroxysmal tachycardia is impending, and quinidine should be administered at once as a preventive measure. Quinidine is the drug of choice in this condition, as vagal stimulation is entirely without effect.

*Delivered before the Saranac Lake Medical Society, November 11, 1936.

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Auricular flutter. Auricular flutter is a less common cardiac emergency than paroxysmal auricular tachycardia and is usually associated with heart disease. It is characterized by the sudden onset of a rapid heart rate in the vicinity of 150 per minute. The rhythm is usually regular, but there may be abrupt changes in rate and sometimes a marked irregularity. The symptoms are the same as in paroxysmal tachycardia. Vagal stimulation causes only a brief slowing of the heart rate. Attacks may be of only a few minutes' or of a few hours' duration, but, if the abnormal rhythm persists for more than a few hours, the patient should be digitalized. Digitalis is effective in two ways in auricular flutter. In the first place, it raises the degree of auriculoventricular block, so that the ventricular rate is slowed and the circulation thus rendered more efficient. At the same time, it usually converts the flutter into fibrillation. If the digitalis is then discontinued, the majority of cases revert to normal rhythm. In those which do not revert under these circumstances, quinidine often proves effective.

Auricular fibrillation. The onset of auricular fibrillation with a rapid ventricular rate not infrequently precipitates failure in a diseased heart and is a signal for prompt digitalization.

Stokes-Adams syndrome. Another disturbance of rhythm that may be considered as a cardiac emergency is the Stokes-Adams syndrome. The Stokes-Adams syndrome is loss of consciousness due to cardiac standstill or an abrupt and marked slowing of the heart rate. When the heart has remained in diastole for more than about 10 seconds, a sudden loss of consciousness occurs as a result of cerebral anemia. The attack may be very transitory and last only a few seconds, and, if the patient is lying in bed, he may be quite unaware of it when he returns to consciousness. More prolonged periods of cardiac standstill are associated with convulsive seizures and sometimes with loss of sphincter control. The more prolonged attacks may be followed by unconsciousness for many hours after the heart rate has returned to normal.

The most simple and effective treatment of the Stokes-Adams syndrome consists of the immediate injection of adrenalin into the heart itself. Since delay of a few minutes might be fatal, no time can be lost in sterilizing a syringe and needle if sterile instruments are not immediately available. A long needle, preferably a lumbar puncture needle, is plunged into the fourth left interspace about 2.5 cm. from the sternal border, and the adrenalin is injected directly into the ventricular muscle or ventricular cavity. Although this is a measure of last resort and is seldom successful, it is occasionally effective in causing resumption of the cardiac rhythm. One is justified in carrying out this procedure in cases of cardiac standstill due to heart block and diminished ventricular irritability and in cases of cardiac arrest during surgical procedures. It is hardly warranted, even as a deathbed gesture, under most other circumstances.

If cardiac standstill occurs during abdominal operations, it is sometimes possible to restore cardiac action by massage of the heart through the diaphragm.

More commonly, the attending physician is presented with the problem of treating repeated attacks of Stokes-Adams syndrome that recur, perhaps, at intervals of only a few minutes. Such cases will respond well to small doses of adrenalin subcutaneously or to ephedrin. This stimulates ventricular irritability to the point where long periods of ventricular standstill become impossible.

MAJOR CARDIAC EMERGENCIES

Acute congestive failure. Let us now proceed to what may be termed the major cardiac emergencies. Under this heading I should like to take up first the problem of acute congestive failure.

In hearts that are diseased but compensated, the addition of a burden, such as infection, fatigue, tachycardia or coronary thrombosis, may precipitate acute congestive failure. Under these circumstances, in addition to any specific treatment of the precipitating factor, certain general, well-tried measures must be promptly and vigorously instituted. The most important of these are rest, digitalis and diuretics.

The word rest must be construed in an absolute sense. Morphine should be given freely. The room should be quiet, and the bed should be comfortable and equipped with a back rest. A nurse should be in constant attendance. Fluids should be restricted to not more than 1,000 cc. in 24 hours, and calories limited at first to about 800.

The presence of acute cardiac congestive failure, regardless of its etiology, is an indication for prompt digitalization. In the majority of cases oral or rectal administration produces rapid enough digitalization, but in patients in whom it seems important to save a few hours, intramuscular or intravenous injection may be resorted to. For intravenous use, the pure crystalline ouabain or strophanthin may be used. In either case, the adult dose is 0.5 mg. if digitalis has not already been used. This may be repeated in 12 hours. Ouabain given intravenously exerts its full effect upon the heart within 1 hour, digitalis by the same route within 2 hours, and digitalis by mouth in about 12 hours. In practice, where quick digitalization is desired, a combination of intramuscular and oral administration is usually satisfactory and safe. For example, in an undigitalized 150 pound man, 9 grains of digitalis may be given in one

dose intramuscularly, together with 6 grains by mouth, followed by 1½ grains every 3 hours until there is either a therapeutic or a toxic effect from the drug. I repeat, however, that the oral or rectal route produces a sufficiently rapid effect in the vast majority of cases and is far safer.

The recently developed, powerful, mercurial diuretics, such as salyrgan and mercupurin, have come to be used relatively early in the treatment of congestive failure and might be considered as emergency treatment in some cases where prompt elimination of the edema is imperative.

Acute pulmonary edema. In addition to the general measures that have been indicated in the treatment of acute congestive failure, there are certain specific procedures that are called for under special circumstances. A particular type of heart failure, which is often encountered, is acute left-sided failure. This is seen particularly in hypertension, aortic regurgitation and advanced mitral stenosis. Failure of the left ventricle to keep pace with the right causes engorgement of the pulmonary vessels and pulmonary edema. Clinically, it is manifested by the onset of dyspnea, which becomes intense, a cough that produces pink, frothy sputum, and marked cyanosis. The lungs are filled with fine and coarse, moist rales. Attacks are often associated with a rise in blood pressure. The object of the various methods of treating acute pulmonary edema is to diminish the flow of blood into the engorged pulmonary circuit. The simplest procedure is the administration of nitroglycerin. This causes dilatation of the peripheral arterioles, which usually results in a diminished peripheral resistance for the left ventricle to work against and, at the same time, in a pooling of blood in the peripheral circuit, which diminishes the venous return to the right heart.

Another simple method of pooling blood in the peripheral circuit is the application of tourniquets to all four extremities, thus hindering venous return. This is often completely successful in relieving an attack.

If these simple measures do not bring immediate relief, a venesection of about 500 cc. should be carried out. In this type of failure the prompt administration of morphine is particularly indicated.

On the whole, the response to treatment of acute pulmonary edema is very satisfactory, and often the change from an apparently moribund condition to one of outward good health is truly dramatic.

Oxygen may be of great benefit in cases where pulmonary edema and cyanosis are present. It is particularly useful in those cases, so commonly encountered, in which there is a combination of heart failure and chronic bronchitis with considerable bronchial secretion. Nasal catheters, if properly applied and watched, are almost as effective for its administration as an oxygen tent.

Acute coronary thrombosis. In general, the emergency measures to be instituted in acute coronary thrombosis are the same as those for acute congestive failure, except that digitalis is not indicated unless signs of failure appear. There are several reasons for being reluctant to prescribe digitalis at the onset of acute coronary thrombosis. In the first place, if one assumes that one is dealing with a heart that is normal except for the infarcted area, there is no reason to think that digitalis would do any good. The evidence is that digitalis decreases the cardiac output in the normal heart. It is only in the dilated and failing heart that digitalis increases the cardiac output. When we consider that the cardiac output in acute coronary thrombosis may be already diminished by the state of shock, which is so frequently associated with its early stages, we feel even more justified in waiting for some other indication for digitalization. Another disadvantage in the use of digitalis in coronary thrombosis is that, in toxic doses, it increases ventricular irritability. Since a large proportion of cases of coronary thrombosis die as a result of ventricular tachycardia and ventricular fibrillation, it is highly desirable not to do anything that might aggravate this tendency. To be sure, the irritating effect of digitalis on the ventricle is not observed until toxic doses are reached; but, if frequent extrasystoles should appear after moderate doses, one might still be in doubt as to whether they were due to the digitalis or to the infarct. If the frequent extrasystoles are being caused by the infarct, one likes to know it, because they may be a precursor of a more serious ventricular arrhythmia.

The occurrence of multiple extrasystoles following coronary thrombosis is an indication for giving quinidine at once in doses of 3 grains three or four times a day to prevent the onset of ventricular tachycardia and ventricular fibrillation. Some authors advocate giving quinidine routinely as a preventive measure in all cases of coronary thrombosis.

Of course, morphine has to be used freely in such cases. Nitroglycerin is useless and may be even harmful, particularly if there has already been a well-marked drop in the blood pressure. Aminophylline has been advocated by some physicians, on the basis that it causes dilatation of the coronary arteries and thereby improves the collateral circulation to the area that was supplied by the occluded vessel and diminishes the size of the resulting infarct. The evidence for this, which is based on experimental coronary ligation in dogs, is not, strictly speaking, applicable to the situation in human coronary occlusion, where positive benefits from its use still await proof. Oxygen is of great benefit in cases of coronary thrombosis if cyanosis is present.

Pericardial Effusion. The occurrence of a large effusion in the pericardial cavity may precipitate an acute cardiac emergency. The commonest causes of pericardial effusion are rheumatic fever, tuberculosis and pneumococcus infection. Considerable amounts of fluid may be accommodated in the pericardium without embarrassing the heart action; and, since the removal of this fluid is attended by a certain risk, the diagnosis of pericardial effusion is not a sufficient reason for tapping. The indications for tapping are, first, situations where a diagnosis is of great importance. This applies particularly to the pericardial effusions that arise in the course of, or immediately following, a lobar pneumonia. The situation is much the same as with the pleural effusions that arise under the same circumstances, except that it is more serious. As with pleural effusion in pneumonia, the pericardial effusion may be sterile and merely an irritative phenomenon. If pus is obtained, however, the pericardium must be opened promptly and drained.

The second and most common indication for tapping the pericardium is mechanical embarrassment of the circulation. When the fluid in the pericardium accumulates to a certain point, it begins to cause pressure on the great veins and to hinder the venous return to the heart—the so-called cardiac tamponade.

The differential diagnosis between pericardial effusion and acute dilatation of the heart may be extremely difficult, even with the assistance of a fluoroscopic examination. If, therefore, one is dealing with a case of rheumatic fever, in which this differential diagnosis is most apt to occur, one should remember the observation of Carey Coombs that pericardial fluid *sufficient to embarrass the circulation* is rare in rheumatic fever.

A lumbar puncture needle with a short bevel makes a satisfactory instrument for pericardiotomy. The approach of choice is just to the left of the xiphoid, with the needle directed upward and to the left. This taps the most dependent portion of the pericardium. Sometimes the accumulation of fluid seems to be almost entirely posterior. In such cases, a puncture through the back over the area of maximal dulness may yield fluid when the anterior approach does not. In cases where cardiac tamponade is present, relief is prompt and dramatic.

Wounds of the heart. A discussion of cardiac tamponade would be incomplete without some mention of wounds of the heart, since death under these circumstances usually results, not from hemorrhage per se, but from the pressure of blood, which escapes within the pericardium, against the great veins. The clinical picture is that of shock with tremendous engorgement of the neck veins and muffled heart sounds. The procedure of opening the pericardium and suturing the wounds of the heart wall has been successfully accomplished in about 75 cases reported in the medical literature.

Stab wounds of the heart, and even small bullet wounds, occasionally result in recovery even without treatment, but many more persons could undoubtedly be saved with prompt surgical intervention. An example of how relatively innocuous a wound of the heart can be is the case of a young man whom I had the privilege of seeing on the service of Dr. Horace Binney at the Boston City Hospital a year ago. He was accidentally shot in the right chest by a .22 caliber rifle bullet. The bullet, which was fired at close range and from the right side of the patient, entered at a point just lateral to the right nipple. There was no wound of exit. He suffered no pain, but there was a moderate amount of bleeding from the wound. He was rushed to the hospital, where he was put under the fluoroscope; the shadow of the bullet was found in the heart shadow, with which it moved and from which it could not be dissociated. The position of the bullet indicated that it was superficially imbedded in the anterior wall of the right ventricle, close to the interventricular sulcus. There was a small hemothorax on the right, but otherwise the patient suffered no apparent ill-effect from his wound; he was discharged from the hospital with the bullet still in his heart after 3 weeks of observation.

Peripheral vascular collapse. I will now say a few words about the emergencies that arise from collapse of the peripheral vascular system, a condition that bears certain superficial resemblances to cardiac collapse and is often mistakenly treated as such.

The clinical picture of shock is one of great prostration, pallor, sweating, pinched features, cold extremities, weak heart sounds, rapid, thready pulse and low blood pressure. Although it appears as a complication of a great variety of clinical conditions, its fundamental mechanism is essentially the same in all. In brief, it may best be described, in the words of Dana Atchley, as "the physiological result of an acute disparity between the circulating blood volume and the functioning capacity of the vascular bed." This acute disparity may result from sudden diminution of the blood volume, such as in massive hemorrhage or from increase in the size of the vascular bed by the effect of toxins in causing capillary dilatation, as in pneumonia. The same acute disparity may result from the loss of serum in extensive burns or in severely traumatized tissue. The loss of water and salts from the gastrointestinal tract from severe diarrhea or from vomiting may bring about the same result. The chief cause of death in diabetic acidosis is shock.

Shock is a common condition in medical practice, and yet it is still frequently unrecognized

and untreated. It is a curious fact that shock has received wider recognition in surgical than in medical practice. The surgeons now realize that when a patient exhibits a fall in blood pressure and a rapid pulse following an operation, it is unlikely that digitalis or any other measures that are directed primarily to the heart will be of any avail. And yet, if the same symptoms appear in pneumonia, they are still apt to be regarded as cardiac in origin and treated as such. Inasmuch as the cardiac output is diminished in shock, the use of digitalis, which would tend to diminish the output still further if the heart were normal, is contraindicated. Digitalis is indicated in pneumonia if auricular fibrillation or myocardial failure is present, but not otherwise. The treatment of shock is relatively simple if we understand the physiologic basis for it. Its object is to overcome the disparity between the volume of the circulating blood and the capacity of the vascular bed that contains it. This can be done by increasing the blood volume or by decreasing the capacity of the vascular bed.

The blood volume may be increased by the intravenous injection of isotonic salt solution and hypertonic glucose solutions or, best of all, because of its more lasting effect, by the transfusion of whole blood.

Our ability to decrease the capacity of the vascular bed is much less certain than is our ability to increase the blood volume. Since depression of the central nervous system is often a contributing factor in the production of shock through loss of tone, stimulants to the central nervous system have been used extensively and with undoubted benefit. The most important of these are caffeine, strychnine and various camphor derivatives. These drugs were long considered to be cardiac stimulants, but it is probable that their therapeutic value lies in their effect on the peripheral circuit, mediated through the central nervous system.

Adrenalin is contraindicated in shock. Its action is to constrict the peripheral arterioles, which are already in contraction, and, although it may cause a temporary rise in blood pressure, it does not tend to correct the underlying physiologic disturbance. Indeed, it may aggravate it.

The patient in shock should, of course, be kept with the head low and in a warm bed with blankets and hot water bottle.

In acute coronary thrombosis we often see signs of shock together with the signs of cardiac failure. In this condition, shock by lowering the systolic pressure and diminishing the venous return tends to lessen the strain on the left ventricle and may, to a certain extent, be a favorable factor.

In closing, I would like to emphasize the fact that acute circulatory failure is as often peripheral as it is cardiac in origin, and adequate treatment of cardiovascular emergencies must depend on a thorough understanding of the mechanism of peripheral vascular collapse, as well as of disorders of the heart itself.

HEART SOUNDS IN PULMONARY TUBERCULOSIS*

BY ALLAN S. KENNEDY, M.B.†

APPROXIMATELY 5 years ago the writer, in making repeat heart examinations on tuberculous patients, became interested in the persistence, in many cases, of whatever type of heart sounds were found at the first examination. It seemed worth while to record at frequent intervals, and over a reasonably extended period of time, the heart sounds on a group of patients who had pulmonary tuberculosis. Clinical statistics were sought in regard to the following problems: (1) the incidence and any general or specific significance of accentuation of the pulmonic and aortic second sounds, either slight accentuation, expressed as P_2 sl.+ and A_2 sl.+, or more marked accentuation, expressed as P_2+ and A_2+, respectively; (2) the relative importance of slight shift of heart position in altering heart sounds as compared with the effect of systemic hypertension, pneumothorax, pulse rate, and so forth; (3) the significance, in terms of general prognosis and in terms of right heart strain, of the reduplication of an accentuated pulmonic second sound, expressed as P_2+ and d.; (4) the possible significance of a reduplicated second cardiac sound at the base, without accentuation; (5) the incidence of left ventricle failure; and (6) the age factor influencing heart sounds.

The clinical material consisted of all patients admitted to the Medical Infirmary from August 21, 1933 to November 1, 1934. The patients were followed until June 1, 1936 or until their discharge. One hundred and fifty-nine cases were studied. At frequent intervals, heart sound, pulse and blood pressure determinations were made in each case. The patient was examined in the supine position. When a heart was classified as being in the left position, no part of it could be seen radiologically to the right of the right lateral border of the

*From the Infirmary for the Study of Medical Conditions Associated with Pulmonary Tuberculosis, Mountain Sanatorium, Hamilton, Ontario.

†Kennedy, Allan S.—Director of the Infirmary, Mountain Sanatorium. For record and address of author see "This Week's Issue," page 766.

vertebral bodies. In the hearts that were shifted to the right, the right transverse cardiac diameter was at least equal to the left transverse diameter. Electrocardiograms were taken in many cases, and phonocardiograms were taken in some of the cases, but not routinely. It would seem, however, that the reduplication of sounds should not be missed or misinterpreted. Certainly the cases listed as examples of accentuation of A_2 or P_2 show a definite accentuation by the graphic method illustrated in figure 1.

There were 22 patients with centrally placed hearts who were 50 years of age or over. The pulmonary lesion was far advanced in 13, moderately advanced in 6 and minimal in 3. There was some accentuation of A_2 in only 8 cases. In 6 of these 8 cases, systemic hypertension* was present. The other 2 patients died, and at autopsy calcification of the aortic valves, and roughening of the aortic valves and atheroma and sclerosis of the aorta were found, respectively. Only 6 of the 22 cases had far-advanced pulmonary tuberculosis and any degree of accentuation of A_2. Five of these had systemic hypertension, and in the other case, calcification of the aortic valves was found at autopsy.

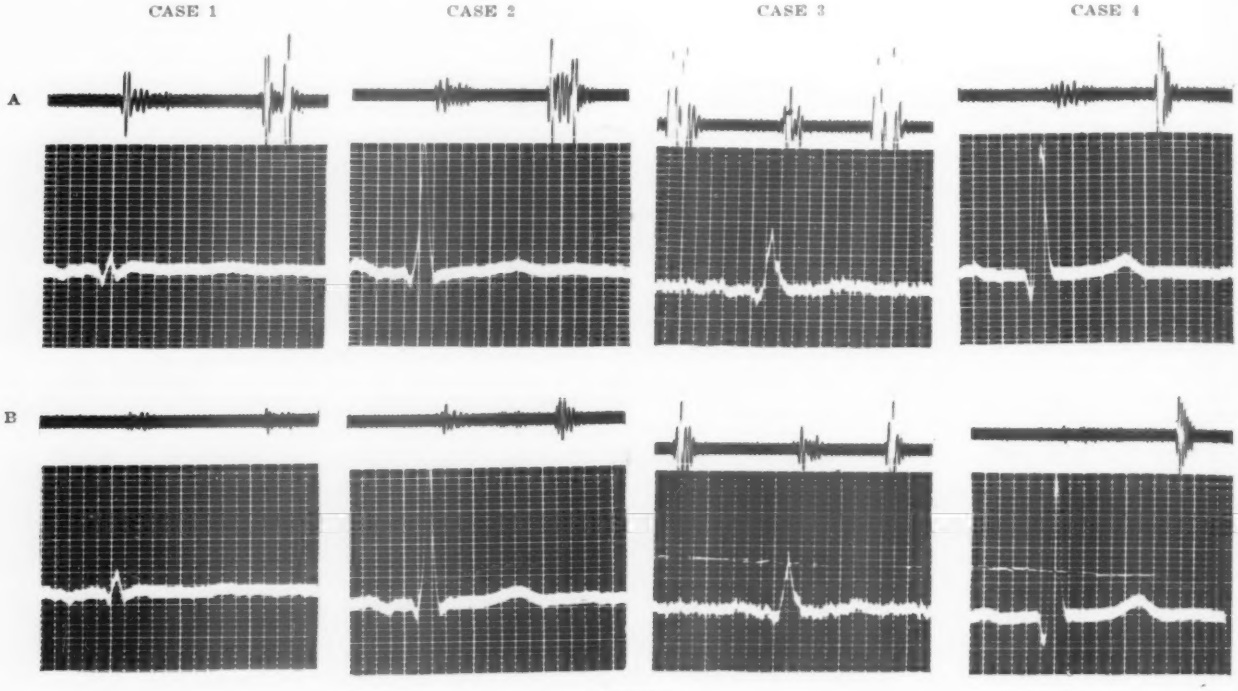

FIGURE 1.

For each case, A shows the record from the pulmonary area of the heart and B that from the aortic area. In each of the 4 cases, P_2 is accentuated. Cases 1, 2 and 3 show reduplication of P_2. Case 4 shows slight accentuation of P_2 but no reduplication. Both first and second sounds are easily identified by reference to the Q-R-S and T waves, respectively, of the accompanying, synchronized electrocardiograms.

TABLE 1. *Relation of Position of Heart and Heart Sounds*

Position of Heart	Number Cases	Heart Sounds				
		P_2+	A_2+	P_2 sl.+	A_2 sl.+	$A_2=P_2$
Central	106	20	16	11	12	47
Left	49	37	1	3	1	7
Right	4	0	4	0	0	0
	159	57	21	14	13	54

Table 1 indicates the effect of heart shift in accentuating the second basal sound on the side to which the shift occurs.

All patients in table 2 had far-advanced pulmonary tuberculosis and centrally placed hearts.

TABLE 2. *Death Rates in Cases with Far-Advanced Pulmonary Tuberculosis*

Heart Sounds	Number Cases	Died	Mortality Per Cent	Autopsies
Accentuated P_2	20	13	65	8
Accentuated A_2	18	7	39	4

In all the deaths in both groups, far-advanced pulmonary tuberculosis must be considered as a factor in the fatal termination. The cases examined post mortem provide data concerning the chief cause of death.

Pulmonary tuberculosis was the chief cause of

*Systemic hypertension means in this paper that the patient had, on at least 6 determinations made over a period of at least 1 month and taken at the same time of day, a blood pressure of 144/80 or higher.

death in 3 of the 8 patients with an accentuated P_2 who came to autopsy. One showed slight hypertrophy and dilatation of the right ventricle. There was 1 case each of amyloid disease and tuberculous meningitis. In 3 cases there occurred failure of the hypertrophied right ventricle.

The other group of far-advanced cases, which numbered 18, showed some accentuation of A_2. In 2 patients there existed a small left-sided pneumothorax, which probably did not materially affect the heart sounds. There were 7 deaths in this group, of which 4 patients were examined post mortem. The causes of death in these 4 were, respectively, left ventricle hypertrophy and failure, lung abscess and multiple emboli of the lung following a rectal operation, pulmonary tuberculosis, and amyloid disease and pulmonary tuberculosis.

From these findings it is evident that the finding of accentuation of P_2 in a patient with far-advanced pulmonary tuberculosis is of real significance in that it may often be found associated with gross evidence of right heart strain.

Mortality rates for the group of 159 patients showed that there was no appreciable difference in mortality based on the following heart positions: central, slightly to the left and markedly to the left. The mortality rates were 35.8, 31.2 and 35.2 per cent, respectively.

Table 3 presents the mortality rates for each group based on differences in the types of heart sounds heard. Three cases with definite rheumatic mitral valve lesions are excluded, as these belong to the central group showing P_2+ and d.

TABLE 3. *Death Rates in Cases with Accentuation of the Pulmonic Second Sound*

Heart Sounds	HEART POSITION: Central			Slightly Left			Markedly Left		
	No. Cases	Deaths	Mort. Per Cent	No. Cases	Deaths	Mort. Per Cent	No. Cases	Deaths	Mort. Per Cent
P_2+ of any degree	28	15	54	28	10	38	17	6	35
P_2+ and d.	2	2	100	5	3	60	10	5	50

Autopsies performed on 5 of the 10 fatal cases showing P_2+ and d. disclosed 2 cases of right ventricle hypertrophy and dilatation. One other case showed dilatation of the right heart and no gross hypertrophy. For any of the given heart positions, the mortality is highest for those cases showing constant reduplication of P_2.

The finding of P_2 reduplication in a case showing a shift of the heart to the left should not be dismissed as being due to heart position but should be regarded as of serious prognostic import; its only relation to heart position is that the shift of the heart to the left probably renders the reduplication more easy to discover.

Seventeen patients had systemic hypertension. Although such cases with central hearts tended to show A_2+, yet a slight shift of the heart to the left, even with marked hypertension, was usually associated with a more audible second sound over the pulmonic area.

Twenty patients had unilateral pneumothorax. It would appear that, unless the pneumothorax causes a shift of the heart to the opposite side and, hence, accentuation of the second basal sound on that side, a considerable blanket of air can exist anteriorly over one side of the chest without appreciably muffling the basal sounds on that side. In 1 case with a left lung that was about 90 per cent collapsed but with the heart held out in the left position by a cord of adhesions, P_2+ was present.

DISCUSSION

It is of some interest to determine statistically the frequency and probable significance of the prevailing heart sounds usually heard in cases of pulmonary tuberculosis. In such cases it is common to find varying degrees of shift of the mediastinum to the right or left. In a tuberculous patient, a slight shift of the heart to the left is associated with an accentuation of P_2, despite the existence of a systemic hypertension, great variation in pulse rate or an appreciable volume of air anteriorly over the left lung from a pneumothorax. Similarly, a very slight shift of the heart to the right seems to be associated with an accentuation of A_2.

In cases of pulmonary tuberculosis associated with a centrally placed heart, the limited statistical data presented above seem to suggest that the finding of A_2+ or P_2+ should be viewed with more attention than if it were an incidental finding as part of the examination of the cardiovascular system of a tuberculous patient.

It appears, from the relatively small number of patients studied, that, in the presence of far-advanced pulmonary tuberculosis and a centrally placed heart, the finding of A_2+ is rather rare at any age, unless it is associated with definite systemic hypertension, calcification of aortic valves or, less frequently, a hypertrophied left ventricle. From the statistics given, it appears that, even in patients over 50 years of age with centrally placed hearts, A_2+ is rarely found in the presence of far-advanced pulmonary tuberculosis where all the factors mentioned above are absent.

P_2+ in cases of far-advanced pulmonary tuberculosis with centrally placed hearts seems to be associated with a higher general mortality rate—a higher death rate from pulmonary tuberculosis and an apparently markedly higher

incidence of right ventricle hypertrophy and failure—than that of cases showing A_2+.

From the total of 159 tuberculous patients presented, there were only 17 who showed a constant P_2+ and d. However, the findings secured from this small group strongly suggest that there is a definitely higher mortality rate in such cases and a higher incidence of gross right ventricle hypertrophy and failure or failure with no gross hypertrophy, than in cases showing P_2+ with no reduplication.

Apparently such reduplication bears a serious significance even when the heart is shifted to the left. In other words, when the heart is shifted to the left P_2+ is to be expected, but when coincidentally a reduplication is heard, the latter finding cannot be justly ascribed to mere position.

In only 3 cases of the 159 was there reduplication of the second basal cardiac sound without accentuation of A_2 or P_2. In all 3 cases, there was reduplication of P_2, and, in 1, the reduplication was also heard over the aortic area. All died, but no autopsies were performed. All 3 had centrally placed hearts.

SUMMARY

1. In cases of pulmonary tuberculosis, a slight shift of the heart position has a marked effect on the heart sounds.
2. In the absence of certain factors, accentuation of the aortic second sound is rare in patients with far-advanced pulmonary tuberculosis and centrally placed hearts.
3. The mortality rates for various degrees of heart shift are given.
4. The mortality rates and the incidence of right ventricle hypertrophy and failure are expressed statistically for two groups of patients with far-advanced pulmonary tuberculosis: (a) those with hearts centrally placed and showing accentuation of the pulmonic second sound and (b) those with hearts central or to the left, who show reduplication as well as accentuation of the pulmonic second sound.
5. The occurrence of pulmonic second sound reduplication without accentuation is mentioned.

I am indebted to Dr. W. S. Stanbury, pathologist at the Mountain Sanatorium, for the autopsy findings in this study.

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THE NEW HAMPSHIRE MEDICAL SOCIETY

THE ONE HUNDRED AND FORTY-SIXTH ANNUAL MEETING

Hotel Carpenter, Manchester, N. H.,
Tuesday and Wednesday, May 18-19, 1937

TUESDAY, MAY 18

ROUND TABLE CONFERENCES

9:30 a. m. D.S.T.

1. *Medicine. Coronary Thrombosis.*
   Thomas M. Dudley, Concord.
2. *Surgery. Persisting Symptoms After Appendectomy.*
   Chester L. Smart, Laconia.
3. *Obstetrics. Work and Plans of the Maternity and Infancy Committee.*
   Robert O. Blood, Concord.
4. *Orthopedics. Fractures.*
   Ezra A. Jones, Manchester.

11 a. m.

1. *Medicine. Pneumonia.*
   Francis H. Nolin, Claremont.
2. *Surgery. Possibilities of Surgery in Rural Communities.*
   M. Dawson Tyson, Hanover.
3. *Ophthalmology.*
   Charles F. Nutter, Nashua.
4. *Dermatology. The Problem of Allergy in Diseases of the Skin.*
   Ralph E. McDonnell, New Haven.

(Members may bring patients to the conference on dermatology.)

2:00 p. m.

GENERAL MEETING

1. *Call to order by the President.*
2. *Symposium on Urology.*
   a. *Some Medical Aspects of the Renal Stone Problem.*
      Fuller Albright, Boston.
      Discussion opened by Nathan T. Milliken, Hanover.
   b. *The Insidiousness of Certain Cancers of the Urinary Organs.*
      E. Ross Mintz, Boston.
      Discussion opened by Elmer J. Brown, Manchester.
   c. *Treatment of Pyogenic Cystitis.*
      Clyde L. Deming, New Haven.

Discussion opened by John C. Eckels, Lisbon.

d. *Transurethral Prostatic Resection vs. Prostatectomy.*
J. Dellinger Barney, Boston.
Discussion opened by John P. Bowler, Hanover.

3. *Recent Advances in the Study of Food Allergy.*
Warren T. Vaughan, Richmond, Va.
Discussion opened by Frank N. Rogers, Manchester and Clarence E. Dunbar, Manchester.

WEDNESDAY, MAY 19

ROUND TABLE CONFERENCES

9:30 a. m. D.S.T.

1. *Medicine. Diabetes and the New Protamine Zinc Insulin.*
Clarence O. Coburn, Manchester.
2. *Surgery.*
a. *Cancer of the Skin.*
b. *Cancer of the Stomach.*
George C. Wilkins, Manchester.
3. *Nose and Throat. Management of the Sinus Patient.*
Raymond H. Marcotte, Nashua.
4. *Pediatrics. Infant Feeding.*
MacLean J. Gill, Concord.

11 a. m.

GENERAL MEETING

The Differential Diagnosis of Jaundice.
Charles Gordon Heyd, New York, President, American Medical Association.

2:00 p. m.

1. *Report of House of Delegates.*
2. *Report of Trustees.*
3. *The Etiology, Treatment and End Results of Gastroduodenal Ulcer.*
Burrill B. Crohn, New York.
Discussion opened by Thomas M. Dudley, Concord and William J. P. Dye, Wolfeboro.
4. *Facts and Fallacies of Organotherapy.*
Anton J. Carlson, Chicago.
Discussion opened by Loren F. Richards, Nashua.

6:30 p. m.

THE BANQUET

Anniversary Chairman
Raymond H. Marcotte, Nashua.
Introduction of Doctor Who Has Been in Practice Fifty Years.
Henry O. Smith, Hudson.
Presentation of Fifty Year Medal
(Nathaniel H. Scott, Wolfeboro).
Introduction of President-Elect.
Introduction of Visiting Delegates.

GUEST SPEAKERS

His Excellency, Francis P. Murphy,
Governor of New Hampshire.
Dr. Frank E. Kittredge,
President, New Hampshire Medical Society.
Dr. Charles Gordon Heyd,
President, American Medical Association.

MISCELLANY

CORRECTION

The following two hospitals should have been included on the list of accredited hospitals in New Hampshire, which was published in the *Journal*, January 21: The Huggins Memorial Hospital at Wolfeboro, and the Portsmouth Hospital.

CANCER

The New Hampshire Cancer Commission has begun a comprehensive program to furnish opportunities for every citizen in the state to ascertain whether he has cancer. Fourteen diagnostic cancer clinics have been established throughout the state.

The New Hampshire advisory committee consists of the following members: Governor Francis P. Murphy, honorary chairman; George C. Wilkins, of Manchester, chairman; Clifton S. Abbott, of Laconia; Ralph E. Miller, of Hanover; James W. Jameson, of Concord; Bishop John B. Peterson, of Manchester; Mrs. Gordon Woodbury, of Bedford; Mrs. Mary I. Wood, of Portsmouth and Mr. Harold Crane, of Manchester. The executive officer or commander of the Women's Field Army in New Hampshire is Mrs. Harry Smith, of Durham.

PERSONALS

Dr. James W. Jameson, of Concord, gave an address before the Laconia Kiwanis Club early in February, on "The Education of the Public Against the Dread and Fear of Cancer." His talk was commended by the Kiwanians for its clearness and its lack of technical terms that the layman finds hard to comprehend.

Dr. George C. Wilkins, of Manchester, gave an address on "Cancer" before a gathering of fifty or more persons at Peterborough, March 10. The program was under the direction of the Women's Field Army of the American Society for the Control of Cancer. Dr. Wilkins has delivered similar addresses before Rotary and Kiwanis clubs, at Plaistow, Nashua, Hampton Center and Dover.

NURSES

The quarterly meeting of the New Hampshire Graduate Nurses' Association was held at Concord, March 10. The principal speaker was Dr. Nels Nelson, assistant director of the Division of Communicable Diseases for the State of Massachusetts.

The title of his address was "A Modern Attack on an Ancient Problem."

At the same time, sectional meetings of the League of Nursing Education were held. Miss Rose E. Griffin, of Hanover, president of the Graduate Nurses' Association, presided over a short business meeting.

Hospitals

The annual North Country Fair, sponsored by the Mary Hitchcock Memorial Hospital at Hanover, was held in the alumni gymnasium on March 5 and 6. An automobile show, commercial displays and an enormous midway with a variety of games were among the features of the two-day program, besides a special entertainment and general dancing to music provided by a band. The concluding highlight on Saturday night was a basketball game between Dartmouth and Princeton.

Clinics

Seventeen Merrimack County patients attended the monthly orthopedic clinic at the New Hampshire Memorial Hospital at Concord, March 11. Dr. Ezra A. Jones, of Manchester, Dr. Warren H. Butterfield and Dr. Donald Barton, both of Concord, were in attendance.

RECENT DEATHS

CARPENTER—Irving L. Carpenter, M.D., prominent local physician and past president of the Manchester Medical Association, died at a local hospital in Manchester on March 15.

Dr. Carpenter was born on April 6, 1866, in Manchester. He attended the Allen School in Newton, Mass., and was graduated from the Harvard Medical School in 1890. He practiced in Sioux City, Iowa, for two years before returning to Manchester where he had been engaged in medical practice for the past forty-five years.

Dr. Carpenter at one time held the office of city physician and also the office of county physician. He held membership in the Manchester Medical Association and the New Hampshire Medical Society. He was one of the few surviving members of the old Manchester Cadets.

He is survived by his widow, Mrs. Ione Carpenter; one sister, Mrs. Edward E. Hoff, of Detroit, Michigan; and two nieces, Miss Emma Elliott, of Brookline, Mass., and Mrs. William Warnock, of Woodbridge, Conn.

GUERTIN—Auguste Louis Guertin, M.D., one of the oldest practicing physicians in Nashua on the point of service, and former Hillsborough County physician, died at his home there on March 7, following a long illness.

A native of St. Hyacinthe, P. Q., he obtained his early education at St. Hyacinthe Seminary and, in 1888, entered Victoria College, known as one of the best surgical institutions of learning on the continent. On April 28, 1892, he received his medical degree at Montreal. The following month he went to West Gardner, Mass., where he practiced for three years. He then moved to Nashua, practicing there until the time of his death.

Dr. Guertin was a member of the Nashua, Hillsborough County and New Hampshire Medical societies.

Survivors include his widow, one son, Alfred Guertin, of Manchester, a brother, Victor Guertin, of Worcester, Mass., a sister, Mrs. Raoul Clappin, of St. Hyacinthe, P. Q., and several nieces and nephews.

RESOLUTION ADOPTED BY THE JOINT COMMITTEE ON HEALTH PROBLEMS IN EDUCATION OF THE NATIONAL EDUCATION ASSOCIATION AND THE AMERICAN MEDICAL ASSOCIATION

Whereas, The eyes and the sight of the school child are of the most vital importance for satisfactory school work, and their preservation for future health and efficiency depends upon their wise conservation during childhood; and

Whereas, The school has a grave responsibility for the conservation of eyesight among school children; and

Whereas, School administrators in many parts of the United States are frequently besieged with demands for admission into their school systems of eye examinations and eye-glass prescriptions by practitioners other than qualified doctors of medicine; and

Whereas, The eye, as an organ of vital necessity, requires careful conservation and deserves treatment only at the hands of trained and competent persons; and

Whereas, Teachers and nurses properly may and often do make rough tests of visual acuity in the classroom, but diagnosis of diseases of the eye and of disturbances of vision requires more extensive examination and often involves treatment other than the mere fitting of glasses; and

Whereas, Even the fitting of glasses often requires the paralysis of accommodation through the use of drugs popularly known as "drops"; now, therefore, be it

Resolved, That it is the sense of the Joint Committee on Health Problems in Education of the National Education Association and the American Medical Association, in meeting assembled at New Orleans, February 23, 1937, that the safety of the eyes of school children, the adequate diagnosis of disease and the correct fitting of glasses require examination of children's eyes (beyond rough visual tests performed by teachers or nurses) by a licensed doctor of medicine and, upon his recommendation, by a medical specialist in diseases of the eye, properly known as an oculist or ophthalmologist.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 23171

PRESENTATION OF CASE

A 46 year old American housewife was admitted complaining of fever and respiratory pain in the right chest.

Five months before entry, the patient had an attack of polyarticular rheumatism, which particularly affected the shoulders. Associated with this attack was considerable fever. Although the acute manifestations subsided, the patient never entirely recovered her strength and continued to become progressively weaker. Two weeks before coming to the hospital, she had a severe chill associated with fever, and a physician stated that there was consolidation of the lung at the right base. After a few days the fever subsided but recurred about 5 days before admission. At this time the physician informed the patient that there were signs of fluid in the right pleural cavity. It was stated that the breath sounds were absent in this region, but the mediastinum was not displaced. She was referred to the hospital for thoracentesis.

Physical examination showed a fairly well-developed but emaciated woman who was evidently ill. The skin was loose, dry and inelastic, and there was a slight malar flush, which was more marked on the right side. There was a healing, crusted, herpetic ulceration of the lower lip. The tongue was heavily furred, and there was slight swelling of the soft palate. Expansion of the right side of the chest was limited, and there was dulness to flatness from the angle of the right scapula to the base. Breath sounds, vocal resonance and tactile fremitus were absent in this region. At the extreme left base, the resonance and breath sounds were impaired. The heart was neither enlarged nor displaced, and no murmurs were heard. The sounds were forceful in character. The blood pressure was 100/60. The remainder of the examination was negative.

The temperature was 102°F.; the pulse 130. The respirations were 32.

Examination of the urine showed a specific gravity of 1.008 and a trace of albumin. The sediment contained large numbers of white blood cells, occasionally in clumps. The blood showed a red cell count of 3,500,000, with a hemoglobin of 55 per cent. The white cell count was 9,200, 83 per cent polymorphonuclears, 10 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils, 1 per cent unclassified cells and 1 per cent lymphoblasts. Search for plasma cells in the blood smear was unsuccessful. There was considerable achromia with moderate variation in the size and shape of the red cells. The blood platelets were said to be definitely increased. The serum protein was 6.6 grams per cent, the calcium 13.2 milligrams per cent, the phosphorus 1.88 milligrams per cent and the phosphatase 5.24 units. Further examination of a urine specimen showed 0.45 milligrams of calcium per cubic centimeter and 0.27 milligrams of phosphorus. A moderate amount of Bence-Jones protein was present in the urine.

An x-ray of the chest showed that the right side of the diaphragm was high and sharply domed. The costophrenic angle was obliterated. The left side of the diaphragm was slightly elevated, and there were a few linear areas of density just above it. The ribs, scapulae and right clavicle showed numerous small, rounded, punched-out areas of diminished density. The acromial end of the right clavicle was almost completely destroyed and exhibited a pathologic fracture. The sixth dorsal vertebra also appeared to be deformed. One rib showed fracture near the vertebra and displacement. A frontal film of the skull showed very little evidence of disease.

On the second hospital day the patient became stuporous, and her temperature rose to 105.4°F. Her condition became rapidly worse, and she died on the following day.

DIFFERENTIAL DIAGNOSIS

DR. JOSEPH C. AUB*: This is the history of a patient with fever who had enough pain in her bones to justify the diagnosis of polyarthritis. Subsequently, she had difficulty in the right chest, which strongly suggests the presence of pleural effusion, although the x-ray proves this to be erroneous. Obviously, she had an infection of some sort, but that is as far as one can go from the history. She obviously had been very ill for 5 months or she would not have lost so much weight.

"Search for plasma cells in the blood smear was unsuccessful." Either that note is put into the record as a red herring or it is important. Obviously they were looking for the signs of multiple myeloma, but plasma cells are not always easily found in that disease.

The chemical blood findings are absolutely characteristic of a parathyroid tumor, that is, a high blood calcium, a low blood phosphorus and a normal total protein. The phosphatase

*Associate professor of medicine, Harvard Medical School; physician-in-chief, Collis P. Huntington Memorial Hospital.

is not elevated, I admit; but in the case of a parathyroid tumor in which the osteoblasts were not actively at work it would be possible to have a normal phosphatase. As a rule, however, a normal phosphatase is against parathyroid tumor.

DR. TRACY B. MALLORY: The protein estimation was done in the routine chemical laboratory, and determinations there average distinctly low. When Dr. Talbott has repeated them, the results are always higher.

DR. JOHN H. TALBOTT: The figure in this case may be as high as 7.5 grams per cent.

DR. AUB: Thank you; that fits in with a plasma cell myeloma. In regard to the calcium excretion in the urine, one must conclude that an elimination of 450 milligrams per liter means the excretion of a lot of calcium. This is also suggestive of parathyroid disease but is not unusual whenever blood calcium is high. The Bence-Jones protein in the urine suggests multiple myeloma, but it may also be present in hyperparathyroidism; and, while it does make one think more of multiple myeloma, its presence does not rule out hyperparathyroidism.

The x-ray findings are surprising. Expecting the presence of pleural effusion, one finds a high diaphragm on the right, which certainly ought not to give all the signs found by physical examination. The thing of chief interest is that the description of the bone lesions sounds characteristic of multiple myeloma. The lesions of this disease are apt to appear particularly in the bones around the chest and in multiple and small punched-out areas. The x-ray findings, therefore, suggest multiple myeloma.

DR. GEORGE W. HOLMES: The very high position of the diaphragm might account for the physical signs. I think that the failure to recognize such a possibility is a fairly common physical error. I do not know the date of the x-ray and, therefore, do not know whether it coincides with the physical findings.

DR. HAMPTON: It was the same day.

DR. HOLMES: That might be the explanation. Too much attention should not be paid to the thickened areas at the costophrenic angle. The process may be of long standing. She may have had pleurisy many years ago, and we do not have to assume that these areas are a part of the present trouble. The heart shadow is a little large. The lesions in the bones are as described. I can add nothing to the description given. I would agree with Dr. Aub that the findings are consistent with multiple myeloma.

DR. HAMPTON: What do you think of the negative skull?

DR. HOLMES: That does not rule it out. We are accustomed to see multiple myeloma involve many bones, but there must be a period when it does not do that. I think the x-rays are against hyperparathyroidism. It should produce decalcification in the bones that are not involved. I should say that these bones are of normal density. The x-rays, so far as such changes are concerned, would be evidence against hyperparathyroidism and in favor of multiple bone tumors.

DR. AUB: This is a puzzling case. May I ask one or two questions?

DR. MALLORY: You may ask them. I do not know whether I can answer.

DR. AUB: Did she have a carcinoma of the breast?

DR. MALLORY: Her breasts seemed normal clinically.

DR. AUB: Did she have fluid removed from her chest?

DR. MALLORY: She was not tapped.

DR. AUB: Then I think one must choose between the clinical picture and the laboratory findings, for these do not agree. If one feels sure of clinical findings, they are often worth more than a casual laboratory finding. Had this patient been in the hospital longer, I would lay more stress on the laboratory findings; but, since she was present for only 21 hours I prefer to pay more attention to the clinical findings.

She had been sick for 5 months with pain in the back and with signs of an infection, which is more apt to occur in multiple myeloma than in hyperparathyroid disease. She had secondary anemia, which makes one think more of myeloma than of hyperparathyroidism. By "multiple myeloma" I mean a neoplasm in her bones. Her blood chemistry, except for one thing,—the low blood phosphatase,—fits in far better with hyperparathyroidism than with anything else. When I started thinking about this case, I thought I had better get together the laboratory data that we had accumulated on various bone tumors. I have collected most of the following data, which I think are illuminating, from a group of cases seen at the Huntington Memorial Hospital.

Blood Analyses in Neoplasia of Bone

	Calcium	Phosphorus	Phosphatase*	Total Protein	Albumin	Globulin
Hypernephroma	14.7	5.6	0.5	7.4	4.5	2.9
(Bulger and Gausman)†	15.0	2.6				
Carcinoma of Breast	14.8	5.2	0.5	7.7		
	11.7		0.3			
Myeloma (plasma cell)	10.0	7.5	0.2	14.9	3.1	11.1
	13.6	5.0	0.2	6.9	3.6	3.3
	10.6					
	10.4	3.5				
	11.6	3.6	0.2			
(Bulger and Gausman)†	15.8	6.5	0.2			
	16.7	4.5				

*Done by Kay's method with normal of 6.2.
†J. Clin. Invest. 12:1135 (Nov.) 1933.

Our case of hypernephroma showed a very high blood calcium, normal blood phosphorus, elevated phosphatase (our normal is 0.2) and normal protein. The patient of Bulger and Gausman had high calcium and low phosphorus.

We had 2 cases of carcinoma of the breast with very high calcium and normal protein. This table indicates to me that the calcium and total protein do not run parallel in metastatic lesions in the bones. In myelomas one can have very high protein and normal calcium (and these results were checked repeatedly) or very high calcium and normal protein. The other characteristic is that all these myelomas have normal phosphatase values, although this is not true of osteogenic sarcoma and is usually not true of metastatic neoplasm with any osteoblastic activity.

This patient has high calcium, normal protein, low phosphorus and normal phosphatase. High calcium and low phosphorus always go with hyperparathyroid disease in my previous experience, although the same findings obtain in Bulger and Gausman's case of hypernephroma. This patient's clinical course is not that of hyperparathyroidism, and certainly the x-rays are not at all characteristic. This x-ray note is that the lesions are those of multiple myeloma with multiple, small, punched-out areas. They exist around the chest cage; they are present in the heads of the long bones, which is characteristic of multiple myeloma; and the skull shows absolutely no decalcification. So, in thinking it over, I will not make a diagnosis of hyperparathyroidism, although I ought to from the blood chemistry. I think this patient had a multiple neoplasm, either multiple myeloma, which I think is the diagnosis, or a breast tumor with multiple metastases to the bones, or hypernephroma with multiple metastases. On account of the blood findings and x-rays of the bones and on account of the fever, I shall make a diagnosis of multiple myeloma rather than of hypernephroma. Hypernephroma would explain everything,—the high diaphragm, the albumin and the bone changes,—but I lean more to multiple myeloma.

Why did she have a fever? Patients with multiple myeloma may have fever, but this woman, it seems to me, must have had an infection somewhere; her temperature would not have been elevated so long (5 months) from multiple myeloma, and she would not have been so obviously very sick. She also had clumped pus and albumin in the urine, though this was probably not observed in a catheter specimen. It is difficult to say where she had infection, but I think she had pus or infection somewhere. The x-ray shows no infection in the chest, but the high diaphragm suggests that this area is possibly involved. I think we must find pus or infection somewhere, and the only place I see to place an infection is under the diaphragm on the right. It then comes down to subdiaphragmatic abscess or perinephric abscess associated with pus in the urine. I think such a diagnosis is a gamble, but so is the diagnosis of multiple myeloma. If she had myeloma, I think she also had pus below the diaphragm, either about the kidney or under the diaphragm.

DR. HOLMES: I would favor myeloma.

DR. HAMPTON: I think it is myeloma.

DR. SIEGFRIED J. THANNHAUSER: I would agree with Dr. Holmes.

CLINICAL DIAGNOSIS

Multiple myeloma?

DR. JOSEPH C. AUB'S DIAGNOSES

Multiple myeloma.
Subdiaphragmatic or perinephric abscess?

ANATOMIC DIAGNOSES

Multiple plasma cell myeloma.
Nephrolithiasis, bilateral.
Secondary anemia.
Thrombophlebitis, both iliac veins, vena cava, left renal vein.
Pyelonephritis, chronic.
Atrophy of the left kidney.
Cholelithiasis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The autopsy on this patient showed multiple bone tumors, and the one at the inner end of the clavicle, when smeared out at the time of autopsy, was obviously composed of plasma cells. We were able to make an immediate diagnosis. Because of the very peculiar blood-chemistry findings, a very careful effort was made to identify the parathyroids; Dr. Castleman and Dr. Cope each spent 2 hours, one took the neck and the other the mediastinum, and an extremely careful search was made. Three parathyroids were found, all of which were perfectly normal. I do not believe a parathyroid adenoma was missed. The chest showed surprisingly little in view of the physical findings, and we can essentially confirm the x-ray. There was a moderate grade of collapse in both lower lobes, and though the prosector thought there was a little pneumonia on one side, the sections failed to show any significant amount.

The kidneys showed an additional finding which, if we had had a kidney plate, would have bothered Dr. Aub even more. She had stones in both kidneys. It is too bad we did not have that information clinically in order to make the case more difficult. The right kidney was markedly atrophied, weighing only 40 grams. The left showed compensatory hypertrophy and weighed somewhat over 200 grams. Both showed a very severe grade of pyeloneph-

ritis. Whether her fever was due to pyelonephritis or to one additional finding, which was not indicated in any way by the clinical information, I do not know. We found that both iliac veins were completely occluded by thrombosis, and this thrombosis extended up the vena cava as high as the mouths of the renal veins, actually entering the left renal vein. There was, without question, a thrombophlebitis, and I think that was probably the source of the fever rather than the pyelitis.

A PHYSICIAN: Did she have a pulmonary embolus?

DR. MALLORY: No.

A PHYSICIAN: Was the high diaphragm due to great distention of the abdomen?

DR. MALLORY: The abdomen was not particularly distended, and I cannot say that we found any reason for the high diaphragm. It seems to me not impossible that the fractured clavicle and ribs and the diminished respiration as a result of pain may have had something to do with it.

A PHYSICIAN: Did she have pleurisy?

DR. MALLORY: Some fibrous pleurisy — no fluid.

DR. HAMPTON: This is the second patient sent into the Baker Memorial Hospital with a question of pneumonia because of pain in the chest and fever on whom a diagnosis of multiple myeloma was made by examination of the chest film.

DR. HIRSH W. SULKOWITCH: To make things more confusing, the stones contained large amounts of phosphates. One other thing may be said. There have been a couple of cases of multiple myeloma with high serum calcium and low serum phosphorus reported in the literature. There have been no similar cases with such blood chemical findings in this clinic. The most important point in the differential diagnosis was brought out by Dr. Aub, that is, that, in spite of extensive bone damage about the chest, she had no decalcification of the skull. She should have shown changes in the skull with that degree of chest involvement, if it had been a case of hyperparathyroidism. In addition, the phosphatase should have been elevated in a case of hyperparathyroidism with a similar degree of bone involvement.

CASE 23172

PRESENTATION OF CASE

A 50 year old Jewish housewife was admitted complaining of bladder trouble.

The patient had been well until 15 months before entry, when she developed dysuria, pyuria and nocturia. There was no associated fever, back pain, flank tenderness or hematuria. She was given medication which caused her urine to become dark in color, but it was never red or bloody. These symptoms continued without any significant change until her entry.

The past and family histories are noncontributory. There was no history of tuberculosis or cancer.

Physical examination showed a well-developed and nourished woman in no acute discomfort. The lungs were clear. The heart was normal. The blood pressure was 120/70. Examination of the abdomen was negative. The kidneys were not felt. Pelvic examination was negative except for a thick, purulent vaginal discharge in which no trichomonas could be found. A cystoscopy showed that the bladder contained thick, purulent urine. The trigone was thickened and velvety, more so in the region surrounding the left ureteral orifice. Scattered over the bladder mucosa were areas of intense redness, and the intervening surface was, for the most part, normal. Ureteral catheters passed to each kidney without difficulty. There was normal flow from both sides, although it was slightly more rapid on the left. The urine from this side was pale and cloudy, and on the right side it was concentrated in appearance. Indigo carmine appeared on both sides with strong color in about 7 minutes. Cystoscopies were done 4 and 7 days later, but on neither of these occasions was it possible to pass a catheter up the left ureter for a distance greater than 3 centimeters. A wax-tipped catheter inserted to the obstructing point showed no scratch marks.

The temperature, pulse and respirations were normal.

Examination of the urine showed a specific gravity ranging between 1.004 and 1.018, with a varying trace of albumin. The sediment was loaded with white blood cells and contained numerous bacteria and an occasional red blood cell per high power field. On one occasion trichomonas were observed, but no tubercle bacilli were seen. Cultures of urine from both kidneys showed *Bacillus coli*. Examination of the blood showed a red cell count of 5,040,000, with a hemoglobin of 85 per cent. The white cell count was 30,700, 96 per cent polymorphonuclears. A blood Hinton test was negative. The blood sugar was 96 milligrams per cent, and the nonprotein nitrogen was 25 milligrams per cent. The serum calcium was 10.7 milligrams per cent, the phosphorus 3.48 milligrams per cent and the protein 6.7 grams per cent.

A retrograde pyelogram demonstrated a catheter extending to the right kidney pelvis, but the other catheter reached only to the midportion of the left ureter. There was a 1.5 centimeter area of calcification in the region of the lower end of the left ureter. This remained in contact with the catheter in all films taken. The injected right kidney, pelvis and ureter were negative. The left ureter was dilated down to the region of the area of calcification, and al-

though the left kidney pelvis was only slightly dilated, it appeared to be distorted. The calices in the region of the lower pole did not fill, and in the same region there were two areas of calcification. An intravenous pyelogram demonstrated a normal right kidney, pelvis and ureter. The lower calices of the left kidney were small and irregular, and there was apparent constriction of the pelvis just distal to the calices. The entire left ureter was dilated down to the bladder, and the area of calcification previously noted lay in the course of the ureter in all films taken. The shadow, however, had the structure of a phlebolith. The two areas of calcification noted in the lower pole of the left kidney in the previous films were still present.

The patient's condition remained unchanged, and on the ninth hospital day an operation was performed.

Differential Diagnosis

Dr. E. Ross Mintz: A history of dysuria, pyuria and nocturia over a period of 15 months unquestionably means chronic urinary infection. It may be limited to the bladder in the form of a chronic cystitis, or the bladder symptoms may be secondary to pathology in the upper tract. Just how long the pyuria had been present is hard to state. We know from the history that it was present for 15 months; but, unquestionably, pus in the urine was present long before the other symptoms came on.

Bladder symptoms such as these may be due to a variety of pathologic conditions. A bladder stone, diverticulum or tumor may give such symptoms. The patient may have a submucous fibrosis, which is not uncommon in a woman of her age. She had a few trichomonas in her urine. It is possible to have a cystitis from trichomonas, but I doubt whether the underlying pathology is due to that.

Cystoscopy showed a chronic infection of the bladder. Thickening of the trigone substantiates the fact that the patient must have had an infection over a long period of time, and the significant fact that the thickening and redness were more pronounced around the left ureteral orifice leads one to suspect that the primary pathology may be present in the left kidney. Both ureters were easily catheterized, but no mention is made as to what the urinary sediment on the left showed. It is stated that the urine on this side was pale and cloudy. I would like to assume that the cloudiness was due to pus and not to phosphates. On subsequent ureteral catheterization, the catheter on the left ascended only 3 centimeters above the orifice. A number of things could happen to cause such a state of affairs. It is possible that the patient passed a small stone after the first cystoscopy, and it is equally possible that enough trauma to the ureter resulted from the first cystoscopy to produce edema in the ureteral mucosa. It may be that the catheter was caught in a fold of ureteral mucosa. The left pyelo-ureterogram showed dilatation of the ureter to a point just above its entrance into the bladder. At this level the 0.5 centimeter area of calcification was seen on the x-ray film. If this is a stone, one would expect that not only the ureter would be dilated, but also the pelvis. However, I have seen a number of cases in which a stone was present in the lower end of the ureter where only a slight dilatation of the pelvis occurred, with a marked dilatation of the ureter. Of course this could account for the catheter not passing up on this side during the second and third attempts.

The distortion of the renal pelvis and the irregularity of the calices may be caused by a number of things. Infection, stone, an extrinsic mass pressing on the pelvis and renal tumor are common causes of pelvic distortion and constriction of calices. The areas of calcification in the kidney substances are worthy of comment. We see calcification a good many times in tuberculosis; it is possible to get calcification in renal tumor; we have seen, in this hospital, renal calcification in patients with parathyroid disease. Every now and then, one sees calcification in the lining of cysts of the kidney. Calcification in diseases such as renal bilharzia and hydatid disease of the kidney should be mentioned but dismissed promptly since these diseases are rare.

Physical examination gives us very little information except that the kidneys were not palpable and that there was no costovertebral tenderness on either side.

The laboratory findings seem to confuse rather than to aid in the diagnosis. I cannot fit in the white cell count of 37,000 with a normal temperature. It seems to me that, with this marked pyuria, the patient ought to have some fever. The white count immediately brings up the question of leukemia, but it does not seem to me that a patient with leukemia would have a red cell count of 5,000,000. A normal serum calcium and phosphorus rule out the presence of parathyroid disease. The fact that no tubercle bacilli were found in the urine means little.

All the symptoms and signs that we have so far point to infection in the left kidney. Constriction of the calices; a dilated ureter, which may be due to infection or obstruction; a history of chronic bladder disturbance; calcification in the lower portion of the left kidney with marked thickening around the left ureteral orifice, would all very well fit in with a diagnosis of kidney infection. It may be a pyelonephritis, a pyelitis or tuberculosis. There is no evidence except renal distortion by pyelogram to support a diagnosis of renal tumor. It is hard to state whether the area of increased density at the

lower end of the ureter is a stone within the ureter or a gland outside it. The patient gave no history of renal colic, and I am inclined more to the feeling that this area is not a stone, although so-called "silent" stones in the ureter are not urologic rarities. I feel that the lesion in the kidney is probably tuberculosis, for the simple reason that the patient has had symptoms for 15 months and also because of the very significant fact that the redness and thickness of the bladder mucosa were quite marked around the left ureteral orifice. This is what we usually see in tuberculosis. It is interesting to note that there was no history of hematuria and that only *Bacillus coli* was obtained from the urine on both sides. A number of cases of tuberculosis have a superimposed infection; I do not know exactly what the percentage is, but I venture to say it is between 15 and 20 per cent.

X-ray Interpretation

Dr. George W. Holmes: This is a plain film of the abdomen before injection, and it shows the shadows described in the region of the pole of the kidney. The kidney is small and it is distinctly smaller than the kidney on the opposite side. A small kidney does not rule out tuberculous pyelonephritis.

It is the left kidney that you are interested in. This film simply shows the other kidney to be normal.

Here is a much better film taken after the intravenous injection of the dye, and it shows a normal kidney on the right and a small kidney on the left side with incomplete filling of the lower calyx, also a dilated and tortuous ureter extending down to the bladder.

Dr. Mintz: It is hard to make a diagnosis of tuberculosis on the evidence of the pyelogram.

Dr. Holmes: The film is more suggestive of a deposit of calcium, but the shadow seems to be in the kidney substance rather than the pelvis.

Dr. Mintz: Stone formation in tuberculosis is not very common.

Dr. Holmes: This film shows a dilated ureter and a shadow which was thought to be a stone.

Dr. Mintz: After seeing the pyelogram I am more convinced that the shadow is outside the ureter and that the reason it was difficult to get the catheter up was because of infection with constriction and narrowing.

Dr. Holmes: I would say that these films are consistent with your diagnosis.

Dr. Mintz: I must admit that when I look at them I do not think they back me up particularly, but I will stick to the diagnosis of renal stones and tuberculosis of the kidneys.

Clinical Discussion

Dr. J. Dellinger Barney: This case offered a good many problems. When the patient came in she had had symptoms for more than 15 months. For 2 years she had been under the care of a very intelligent doctor who had tried everything on her without effect. She was very miserable, with frequent dysuria, and had been on the bed pan day and night for several weeks. Physical examination was essentially negative so far as any kidney stone was concerned, but when I looked into the bladder I saw what we call a "light-absorbing" bladder—normal areas that did not light up freely, areas of intense redness, some of which I think were ulcers, on the left side. This happened on two or three occasions. There was no question but that the redness and the velvety condition of the mucosa on the left were markedly increased over that on the right side, which suggested tuberculosis. On at least one occasion I got the catheter up the ureter without any trouble, but I did think this shadow which you have seen in the film looked like a stone. So I did another cystoscopy but was unable to get the catheter up. It was probably harder because of the fact that the bladder was irritable, and I could not do first-class work. Later I gave her spinal anesthesia and did it without trouble.

We had stereoscopic films of the catheter and ureter, and we also passed a wax-tipped catheter, all with negative results. The diagnosis of stone in the ureter, while pretty seriously considered at first, was eventually ruled out. The fact that she had colon bacillus infection of both kidneys did not deter me from my final diagnosis, which was tuberculosis with calcification of the left kidney, and which was so recorded at operation. Because it is a fact that, with renal tuberculosis, the catheter urine is quite frequently sterile, we have been taught that sterile urine is rather characteristic of tuberculosis of the kidney. That is true in a certain percentage of cases; I do not know just what the figures are, but there is a certain amount of infection from the colon bacillus if the patient has been catheterized or instrumented. A healthy kidney is much more likely to have secondary infection than a tuberculous kidney, although again I cannot recall the percentage. But in this case the tuberculous kidney was also infected. The diagnosis was made partly by ruling out this shadow here as being a stone and partly by the peculiar filling defect involving the lower portion of the pelvis and calices of this kidney. Obviously there was some sclerosing, inflammatory process going on which shut the lower calices and the lower half of the pelvis out of the picture. The appearance of the bladder around the left ureter and possibly stricture of or narrowing of the ureter in spots—all these facts, together with her symptoms, made me make a preoperative diagnosis of renal tuberculosis.

At operation the kidney looked uncomfortably normal. For a long time I could not see any evidence on the outside that it was involved. It was a very normal-looking kidney in size, color and consistency, but posteriorly there were two or three white nodules which were very suggestive of tubercles. In addition, the ureter itself was thick, stiffened, dilated, and more or less adherent. The ureter is a pretty good guide in renal tuberculosis. It is very frequently infected. I remember Dr. Hugh Cabot saying that one could often make a diagnosis by the appearance of the ureter. Dr. Smith, you will remember that we used to cut down on the ureter near the pelvic brim extraperitoneally to look at it and to withdraw urine from it with a needle and syringe. This was in the days before intravenous pyelography and in cases where we could not find the ureter by cystoscopic examination.

This was a puzzling and a very interesting case. The unfortunate part of it is that, like so many of these cases, her bladder symptoms still bother her. I am at my wit's end, and her doctor has tried everything he knows, but she still has pain. Later it may be necessary to transplant the healthy ureter into the colon.

Preoperative Diagnosis

Renal tuberculosis.

Dr. E. Ross Mintz's Diagnoses

Tuberculosis of the left kidney.
Nephrolithiasis.

Anatomic Diagnoses

Tuberculosis of the left kidney.
Nephrolithiasis.

Pathological Discussion

Dr. Tracy B. Mallory: The kidney that was removed was slightly smaller than normal and, despite the nearly normal external appearance which Dr. Barney has described, showed very extensive tuberculosis on section. The parenchyma contained both caseous and purulent foci, and the tips of the pyramids were eroded. The calices and pelvis were markedly deformed by scar tissue, and the involvement extended down the entire length of the 7 centimeters of ureter that was resected. A small stone was present in one calyx and undoubtedly was responsible for the calcification noted within the kidney outline by the roentgenologist.

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MAY DAY — CHILD HEALTH DAY

SINCE 1928, when, in accordance with the Congressional Resolution of May 18, the president was authorized to proclaim May Day as Child Health Day, this date has been officially set aside to promote the extension of year-round child-health services in every community, including services for physically handicapped children.

In carrying out this objective, state May Day chairmen are appointed by state health officers, and state departments of education are asked to cooperate by planning and directing school Child Health Day programs. These programs include an evaluation of child-health services in the communities, the launching of new local child-health projects, and exhibits or programs celebrating gains made. For the children themselves, festivals, athletic contests and exhibits celebrating their growth, vigor and safety from health hazards are planned.

Child Health Day has been recognized in Massachusetts for eleven years by the distribution of material for school and community celebrations, and many school systems have incorporated in their regular health programs an annual May Day celebration, which is an especially appropriate way for climaxing the year-round program. The present tendency is for individual room or school celebrations rather than the spectacular pageants and field days so popular several years ago. In these programs our Department of Education, together with the Department of Public Health, has also encouraged the cooperative efforts of groups of small rural schools to join together under good social and health conditions in the playing of many types of organized games.

Community celebrations of Child Health Day are often planned for a community-wide focus on health for a day or even for a week. The fraternal, social and patriotic organizations have speakers on health topics, the merchants plan window displays of health-promoting products, and in the churches the president's and governor's May Day proclamations are read. Some communities use this celebration for the launching of some definite health program, others for the drive for funds for the support of visiting nursing associations.

In relation to this whole subject of child health, it may be pertinent to mention the excellent organization of the Division of Child Hygiene of our Department of Public Health, which has been so active and so successful in promoting the ideals of the Children's Charter.

TULAREMIA

THE etiologic agent of tularemia, *Bacterium tularense*, was first described by McCoy in 1910 as the cause of a plague-like disease of ground squirrels in Tulare County, California. Since then, according to Francis[1] of the United States Public Health Service, as high as 1 per cent of wild cottontail and jack rabbits and snowshoe hares in certain localities of the United States have been found to be infected. Over 90 per cent of the human cases of tularemia follow the handling of such animals, and an appreciable number of human beings are infected from the bites of bloodsucking ticks and flies[2]

that have previously fed on animals infected with *Bacterium tularense*. Other cases have been reported following the dressing or bites of other rodents and even from the dressing of birds, such as the quail and the sage hen. The bacterium has been isolated from the ruffed grouse and sharp-tailed grouse in Minnesota, though no human infections following contact have been noted. The seasonal incidence of the human disease depends upon the source of the infections. The dates of onset of cases east of the Mississippi, following the dressing of wild rabbits, are confined almost entirely to the "open season",—November to January, inclusive,—whereas the cases following bites of ticks or flies in the western and southern areas are limited to the spring and summer months.

The New England States and others in the northeastern section of the United States are fortunate in that their native rabbits, the cottontail and the snowshoe hare, are not infected with *Bacterium tularense*. For the twelve-year period, 1924 to 1935, inclusive, according to Francis, a total of 6,174 cases of tularemia with 299 deaths were reported in the United States. Of this number only 4 cases occurred in New England—a case in Massachusetts, New Hampshire, Maine and Rhode Island, —and 31, 91, 14 and 3 cases were recorded in New York, Pennsylvania, New Jersey and Delaware, respectively. Furthermore, of the 138 cases with a definite history reported in the states mentioned above, 104 followed contact with "market rabbits" shipped from western and southern localities and held in cold storage, or with rabbits killed in southern states.

Of the remaining 34 cases, 30 occurred following the dressing of native wild rabbits killed in sections of Pennsylvania, New Jersey and Delaware that are in close proximity to Maryland, Ohio and Virginia where infection is relatively common—during this same period 185, 586 and 550 cases were reported, respectively, in the latter three states. The other 4 cases followed dressing native rabbits (New Hampshire and Rhode Island), a deer (New York) and a red fox (Maine).

Although the rabbit population of New England is apparently either resistant or has not been grossly exposed to infection with *Bacterium tularense*, the possibility of human infection from this source or from "market rabbits" should not be overlooked by the practicing physician. During the last week of December, 1936, 9 cases of tularemia with 3 deaths were reported to the Department of Health of New York City. In two instances the patients acquired the infection outside the state, but in all the other cases the patients gave a history of handling or dressing "market rabbits."

This brings up the question of the advisability of importing live western rabbits for restocking the depleted native rabbit population, as practiced by the game commissions of New York and Pennsylvania and, to a less extent, by that of Connecticut. This practice has not resulted in infection of the native wild rabbits in New York or Connecticut, for, as yet, no case of tularemia has been reported in which infection followed the handling of rabbits killed within the confines of either state. The reason for this noninfectibility is not clear. Is the native rabbit population of the northeastern section of the United States naturally immune to infection with *Bacterium tularense* or is the low incidence of the common vectors — rabbit ticks, lice and fleas — responsible? Until more is known, the proposed restocking with western rabbits by the Massachusetts Division of Fisheries and Game should be discouraged. This attitude has been taken by former directors and should be continued in fairness to the health of the rabbit and, secondarily, to that of the human population.

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THE FLOWERS THAT BLOOM IN THE SPRING, TRA LA!

A FASCINATING novel, "Three Fevers," by Leo Walmsley, tells of the three perennial and seasonal fevers that epidemically seize the inhabitants of a little fishing village in the north of England and upon the North Sea. At one time of year it is codfishing; at another lobster trapping; and at a third salmon netting: and so repeat. These are, however, not diseases that affect the hardy fishermen and their mates, but rather emotional disturbances that spur them on to new and varied activities, dependent on the seasonal harvest that the sea presents, and the demands of the London market.

We are now told by the Northwestern National Life Insurance Company, in a recent bulletin, that neither is spring fever a disease. The implication is that spring fever is a "condition", partly emotional, perhaps, but partly due also to the effect of a warm environment on a body that has become adjusted to a cold one. The body in winter, according to this thesis, develops energy to battle against chilly temperatures by the use of more and heavier foods. With the crocuses, but particularly with the daffodils, comes that tired feeling, and the only cure is a prompt change to a warm weather diet with more salads, fruits and vegetables than had been ingested when skiing was the method of locomotion of choice.

Some even, in the spring, when that let-down feeling assails them, seek out the lowly dandelion green as if by instinct, filled as it is with minerals and burgeoning with rich, succulent vitamins. And for each dandelion that is decapitated, five more will spring from its tenuous, tapering root, thus insuring the perpetuation of the human race, if not of a velvety lawn.

We are told, however, that, if that tired feeling is accompanied by a true hyperpyrexia, it is not spring fever; the doctor had better be called.

THIS WEEK'S ISSUE

CONTAINS articles by the following named authors:

ALBRIGHT, FULLER. M.D. Harvard Medical School, 1924. Associate physician, Massachusetts General Hospital. Associate professor of medicine, Harvard Medical School. Address: Massachusetts General Hospital, Boston.

BUTLER, ALLAN M. M.D. Harvard Medical School, 1926. Associate visiting physician, Infants' and Children's hospitals, Boston. Associate, department of pediatrics, Harvard Medical School. Address: Children's Hospital, Boston.

HAMPTON, AUBREY O. M.D. Baylor University College of Medicine, 1925. Assistant roentgenologist, Massachusetts General Hospital. Instructor in roentgenology, Harvard Medical School. Address: Massachusetts General Hospital, Boston.

SMITH, PATRICIA. M.D. Boston University School of Medicine, 1936. Medical intern, Johns Hopkins Hospital, Baltimore, Md. Address: Johns Hopkins Hospital, Baltimore, Md. Their subject is "Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females." Page 727.

FAULKNER, JAMES M. M.D. Harvard Medical School, 1924. Instructor in medicine, Harvard Medical School. Junior visiting physician, Boston City Hospital. Visiting physician, House of the Good Samaritan. Address: 264 Beacon Street, Boston. His subject is "The Treatment of Cardiovascular Emergencies." Page 747.

KENNEDY, ALLAN S. M.B. University of Toronto, 1927. Director of the Infirmary for the Study of Medical Conditions Associated with Pulmonary Tuberculosis, Mountain Sanatorium. Associate, American College of Physicians. Address: Mountain Sanatorium, Hamilton, Ontario. His subject is "Heart Sounds in Pulmonary Tuberculosis." Page 751.

The Massachusetts Medical Society

ANNUAL DISCOURSE

THE Annual Discourse of the Massachusetts Medical Society will follow the business meeting called to order at twelve noon, Thursday, June 3, in the Lobby Salon of the Hotel Bradford and will be delivered by Dr. Joseph W. O'Connor, visiting obstetrician, the Memorial Hospital, Worcester.

Dr. O'Connor's subject will be "The Medical Society and Maternal Mortality."

SECTION OF OBSTETRICS AND GYNECOLOGY*

R. S. TITUS, M.D., *Chairman*, 472 Commonwealth Ave., Boston, Mass.

R. J. HEFFERNAN, M.D., *Secretary*, 1101 Beacon St., Brookline, Mass.

CASE HISTORIES

No. 17. CHORIO-EPITHELIOMA

Mrs. A. T. S., a secundigravida, aged 31 years, was first seen in consultation December 5, 1935. She had been married 4 years; her family history was negative. The patient was said to have been a "bleeder" as a child. She had pneumonia some years previously, and her tonsils were removed 5 years ago. Her basal metabolic rate had been as low as minus 20. Her catamenia began at 13; her periods were regular, occurring every 30 days, the flow lasted 5 to 6 days, and she used four napkins a day for 2 days. She had a miscarriage 3 years previously, which was possibly related to overexertion.

*A series of selected case histories by members of the Section will be published weekly.

Comments and questions by subscribers are solicited and will be discussed by members of the Section.

She had not had a dilatation and curettage following the miscarriage. She was in bed 4 days, and her convalescence was uncomplicated. There was a normal full-term pregnancy in 1934. During that pregnancy there was moderate nausea and vomiting, which lasted 3½ months and was accompanied by a 15 pound weight loss. During the remainder of her antepartum period there was reasonable weight gain, and the blood pressure and urine were normal. She was delivered at term of a moderate-sized baby by low forceps, and her convalescence was uneventful.

Her last catamenia began August 6, 1935. She first consulted her obstetrician on October 15. She stated then that on October 5 she had suddenly flowed about 3 teaspoonfuls of bright blood without known cause. There was no more bleeding after that episode up to the time of her first visit. There were no cramps. There were nausea and vomiting for 2 weeks. At this time her blood pressure was 90 systolic and 60 diastolic, and the urine was negative for sugar and albumin. The general physical examination was negative, and the pelvic examination showed the uterus to be enlarged to the size of a 2 months' pregnancy, 2 to 3 degrees retroverted, with the cervix in descent almost to the introitus.

In November the nausea and vomiting became more exaggerated, and acetone appeared in the urine, varying from 1 plus to 3 plus. She was put to bed where she remained until her entrance to the hospital. The vomiting became less marked under a dietary regime, catharsis and enemas, but during this period there were times when there was slight vaginal bleeding. The bleeding was never profuse but rather exaggerated staining. The blood pressure was subnormal during this time, and the urine showed the slightest possible trace of albumin in addition to the acetone. It was not until the end of November that it was apparent that the uterus was enlarging beyond her computed dates, it being then about the size of a 6 months' pregnancy, rising to the level of the umbilicus. Prior to this time, the enlargement, although greater than that indicated by the computed dates, did not give concern. Fetal motion had not been felt. No abnormal elements were found in the staining on the pads.

On December 5, the patient was removed to the hospital where she was seen in consultation. An x-ray showed no fetal elements. There was only a "large pear-shaped shadow extending from the pelvis to the fourth lumbar vertebra." An Aschheim-Zondek test, quantitated, showed a positive reaction in a 1 to 64 dilution. The urine showed a very slight trace of albumin, no sugar and many white blood cells in the sediment. The hemoglobin was 68 per cent, and the red blood cell count 3,800,000.

It was decided to empty the uterus, since the presence of a hydatidiform mole appeared evident. This was done on December 5 by packing the cervix with a strip and two catheters. The mole was passed in the next 18 hours, and a few hours later a curettage was done. At this time, much additional tissue was obtained; the uterine canal was deep, but the walls were not unreasonably soft. Dull curets were employed. Ergot and pituitrin were administered. Two days later there was a slight chill, and her temperature rose to 102.8° F. The temperature receded within a week. An Aschheim-Zondek test on a urine specimen obtained immediately after the curettage was reported negative by one laboratory but the report from another laboratory, on a specimen taken December 10, was positive in a dilution of 1 to 128.

Pathological report of mole removed on December 6. "Hydatidiform mole weighing 640 grams consisting of typical, pale, translucent vesicles. Chorionic sac opened. No amnion found. The curettings showed fragments of endometrium of hyperplastic decidual type. They consisted of a large handful of tissue, chorionic vesicles and decidual tissue. The specimen represented a pathologic ovum consisting of a ruptured empty chorion showing marked hydatid degeneration. Microscopic examination showed villi varying from those of normal appearance with loose stroma to large vesicles with edematous stroma. The chorionic epithelium on the surface of these hydatid villi was fairly regular, but there were many instances of piled-up, proliferated areas consisting of both Langhans and syncytial elements. The Langhans elements showed mitoses but were well differentiated. There was no evidence of invasion of maternal tissue by fetal elements." (Fig. 1.)

During her convalescence from the curettage the patient continued to bleed but not enough to cause apprehension. At times the bleeding diminished, and it was felt after further consultation that the uterus should again be explored for diagnosis and the curettings studied. The red blood cell count, which had been 3,800,000 on December 5, decreased gradually to 2,900,000 on December 23, but after that date there was a gradual rise until January 2, when the count was 4,170,000.

The diagnostic curettage, done on January 8, caused apprehension at the time it was performed since the canal seemed deep and the tissue beneath the curet extremely soft and friable. There was great concern that the uterus might be perforated with the slightest maneuver. However, a certain amount of tissue was obtained. There was no undue hemorrhage, and the patient showed no evidence of shock.

Pathological report of curettings removed on January 8. "Actively growing, undifferentiated, chorionic epithelium together with a few

hydatid villi. Viable, chorionic epithelium unattached to a villus. Large amount of hemorrhagic material surrounding the epithelium. Slides showed masses of actively growing hyperplastic and undifferentiated chorionic epithelium. Syncytial types of cells with mitoses were present. Relatively large amounts of undifferentiated, moderately rapidly growing chorionic epithelium in sheets and masses. Diagnosis: chorio-epithelioma." (Fig. 2.)

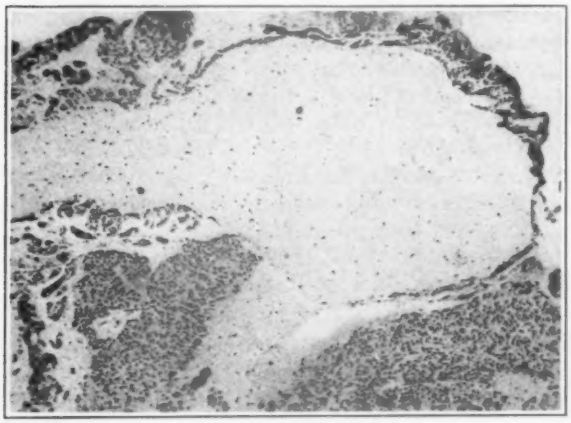

FIG. 1. Curettings showing a hydatid villus with large sheets of proliferating anaplastic trophoblastic cells mainly of the Langhans type, with occasional syncytial buds and masses. Hematoxylin and eosin ×40.

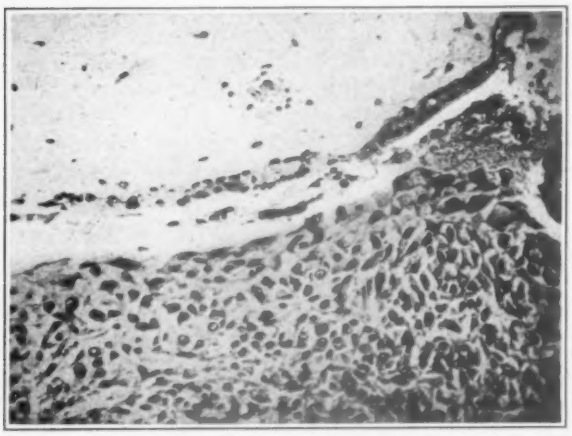

FIG. 2. A high power view of curettings showing sheets of trophoblastic epithelium composed mostly of Langhans cells. Covering these is a layer of syncytial-like epithelium. Hematoxylin and eosin ×110.

Prior to panhysterectomy, which was done January 13, a transfusion was performed in which 600 cc. of citrated blood was given. The husband and wife were compatible. It was considered inadvisable to leave the ovaries in situ because of the possibility of metastases.

A medical consultation prior to the operation revealed no contraindication to operation. The hysterectomy was uncomplicated. A vaginal drain introduced at the operation was removed on the fourth day. Convalescence was remarkably smooth with very little febrile reaction, and the patient was discharged home in 2½ weeks.

Pathological examination of uterus, tubes and ovaries. "At the fundus was a sloughing, yellowish-grey, irregular, ulcerating area with indurated margins representing a placental site. Near one margin of this area the uterine wall was thinner and more fluctuant, and, on section, this was seen to be due to invading villi. The ovaries showed simple cysts. Sections disclosed malignant, invasive, chorionic epithelium within the myometrium. Mitoses were present. Diagnosis: chorio-epithelioma." (Figs. 3 and 4.)

FIG. 3. Placental site from invasive malignant mole. Note the presence of large masses of undifferentiated Langhans cells in vascular sinusoids. There are occasional syncytial elements around the periphery of the Langhans masses. Hematoxylin and eosin ×40.

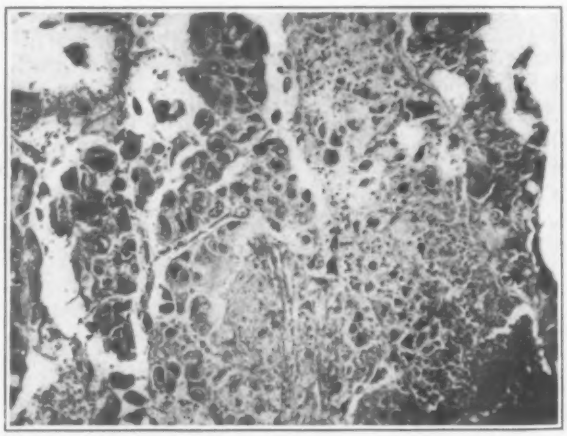

FIG. 4. A high-power view of the same showing invading trophoblast cells, which are anaplastic and show large, irregular, hyperchromatic nuclei.

The Aschheim-Zondek test was positive on January 14, and there was a positive Friedman test on February 6. Aschheim-Zondek tests done on February 21, April 16 and November 7 were all negative.

When seen in the office on November 11, 1936,

the patient was having mild menopausal disturbances. There was no pain or discharge of any kind, and her weight had returned to normal. Pelvic examination revealed a normal panhysterectomy pelvis without any masses, tenderness or bleeding.

The patient was advised to submit to a pelvic examination and to have an Aschheim-Zondek test done every month for a year.

RECENT DEATHS

JANES—Benjamin Franklin Janes, M.D., of 211 Elm Street, Northampton, died suddenly April 17. He was in the fifty-second year of his life.

A native of Boston, Dr. Janes spent part of his early years in Nantucket. He was graduated from Tufts College Medical School in 1908 and set up practice in Northampton two years later. During the World War he served overseas as a captain in the medical corps.

He was a member of the Massachusetts Medical Society, the American Medical Association, the American Legion, the Kiwanis Club and the Masonic Order.

His widow, Mrs. Ruth L. Janes, and two sons, Benjamin F. Janes, Jr., of the United States Navy, and Lee S. Janes, a student at Tufts College, survive him.

ROSEN—David W. Rosen, M.D., of 79 Elm Avenue, Roxbury, died January 3.

Dr. Rosen was born in 1880 and was graduated from Tufts College Medical School in 1910. He was a member of the Massachusetts Medical Society and the American Medical Association.

WOODILL—Edith Esty Woodill, M.D., of Waverley, died February 27.

She was graduated from Tufts College Medical School in 1904 and for several years had been connected with the Walter E. Fernald State School in Waltham. She was a member of the Massachusetts Medical Society, the American Medical Association and the New England Society of Psychiatry.

NOTICES

REMOVAL

Frank A. Pemberton, M.D., announces the removal of his office to 330 Dartmouth Street, Boston. Telephone: Kenmore 0322.

NATIONAL HOSPITAL DAY

The Quincy City Hospital is making extensive plans for the celebration of National Hospital Day. The program to date is as follows:

May 6 and 7. Visit to the hospital by the clergy of Quincy.

May 8. Hospital Day for the children of Quincy from 10 a. m. to 12 m.

1. Hospital moving pictures.
2. Awarding of essay contest winner on the subject, "How Doctors and Hospitals Protect Your Health."
3. Demonstrations and music.

May 9. Announcement of National Hospital Day in the churches of Quincy. Church services for the hospital personnel.

May 10. A combined luncheon meeting of Kiwanis and Rotary clubs at the hospital. To be shown a lay picture on the subject, "Appendicitis."

May 11. Hospital employees' party at the hospital. Hospital moving pictures and music.

May 12. National Hospital Day. Inspection of and demonstrations by the various hospital departments.

Open house from 1 to 4 p. m.

7:30 p. m. Dedication of new administration building. Dedicatory exercises and music.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The annual meeting of the Massachusetts Society of Examining Physicians will be held at the Hotel Copley Plaza, Wednesday, May 5. Dinner will be served at 6:30 p. m. ($2.50 per plate) and will be followed by a memorial meeting to the late Dr. Francis D. Donoghue, founder of the Society.

SPEAKERS

The Honorable Joseph A. Parks, chairman, Massachusetts Industrial Accident Board.

Judge Frank J. Donahue, former chairman, Massachusetts Industrial Accident Board.

Edward E. Clark, Esq., former member, Massachusetts Industrial Accident Board.

Dr. Frederic J. Cotton.

Dr. William J. Brickley.

Dr. William Edward Browne.

Bernard A. Godvin, M.D., *President*,
William Pearce Coues, M.D., *Secretary*.

FAULKNER HOSPITAL CLINICAL MEETING

The final meeting of the year will be held on May 6. In addition to the usual clinicopathological conference, Dr. Reginald H. Smithwick will talk on "Surgical Treatment of Essential Hypertension." All physicians are invited.

AMERICAN HEART ASSOCIATION

The thirteenth scientific sessions of the American Heart Association will be held on June 7 and 8 from 9:30 a. m. to 5:30 p. m., in the Viking Room, Hotel Haddon Hall, Atlantic City, New Jersey. On Monday, June 7, the program of the Section for the Study of the Peripheral Circulation will be given. The general heart program will be presented on Tuesday, June 8.

NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held at the Evans Memorial, Mass-

achusetts Memorial Hospitals, Boston, Monday, May 10 at 8:15 p. m.

PROGRAM

1. The Reaction of the Heart During Work; Cardiopulmonary Function Tests.—Gustav Nylin, M.D., associate professor of medicine, Royal Caroline Institute, Stockholm.
2. An Attempt to Treat a Case of Subacute Bacterial Endocarditis by Surgery.—Ashton Graybiel, M.D., and John W. Strieder, M.D.
3. A Possible Instance of Paroxysmal Auricular Fibrillation of Cerebral Origin.—Norman Boyer, M.D.
4. The Multiple Stethoscope: Is It a Useful Implement for the Clinical Teaching of Heart Disease?—Reginald Fitz, M.D.
5. On the Management of Obesity in Relation to the Treatment of Heart Disease.—Ben Vidgoff, M.D.
6. An Unusual Case of Thoracic Aneurysm.—Harry Parks, M.D.

All members of the New England Heart Association and interested physicians are invited to attend.

JAMES M. FAULKNER, M.D., *Secretary.*

BOSTON SOCIETY OF ANAESTHETISTS

The regular meeting of the Boston Society of Anaesthetists will be held at the Hotel Kenmore, Tuesday, May 4, at 8:30 p. m.

Speaker: Dr. Albert Miller, of Providence, Rhode Island.

Subject: Postoperative Pulmonary Complications.

Physicians and medical students are cordially invited to attend.

E. B. FERGUSON, M.D., *Secretary.*

BOSTON DISPENSARY

25 Bennet Street, Boston
Lecture Hall, Second Floor—9-10 a. m.
May, 1937

MEDICAL CONFERENCE PROGRAM

Saturday, May 1 — Hospital Case Presentation. Dr. S. J. Thannhauser.

Tuesday, May 4—Diagnosis and Treatment of Certain Hip Conditions. Dr. John D. Adams.

Wednesday, May 5—Hospital Case Presentation. Dr. Robert W. Buck.

Thursday, May 6—Some Considerations in the Diagnosis and Treatment of Syphilis. Dr. William A. Hinton.

Friday, May 7—Hospital Social Service; Its Origin and Development. Dr. Richard C. Cabot.

Saturday, May 8—Hospital Case Presentation. Dr. Robert W. Buck.

Tuesday, May 11—Dizziness from the Aural Standpoint. Dr. Philip E. Meltzer.

Wednesday, May 12—Hospital Case Presentation. Dr. S. J. Thannhauser.

Thursday, May 13—Class Method of Treatment of Hypertension. Dr. Robert W. Buck.

Friday, May 14—Mind and Matter or the Psyche and the Heart. Dr. Paul D. White.

Saturday, May 15—Hospital Case Presentation. Dr. S. J. Thannhauser.

Tuesday, May 18—Some Thoughts on the Functions and Possible Pathological Significance of the Renal Nerves. Dr. G. Philip Grabfield.

Wednesday, May 19—Hospital Case Presentation. Dr. S. J. Thannhauser.

Thursday, May 20—Cardiac Irregularities in Bacterial Endocarditis. Dr. Maurice S. Segal.

Friday, May 21—The Origin and Nature of Complications of Scarlet Fever. Dr. Conrad Wesselhoeft.

Saturday, May 22—Hospital Case Presentation. Dr. S. J. Thannhauser.

Tuesday, May 25 — X-Ray Demonstration. Dr. Alice Ettinger.

Wednesday, May 26—Hospital Case Presentation. Dr. S. J. Thannhauser.

Thursday, May 27 — Social Service Case Presentation Mrs. H. B. Hooker, Miss Elizabeth Grundy.

Friday, May 28 — The Effects of Emotion on the Body. Dr. Walter B. Cannon.

Saturday, May 29—Hospital Case Presentation. Dr. S. J. Thannhauser.

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, MAY 3

Monday, May 3—

*4 p. m. Physicians and medical students are cordially invited to attend a clinic presented by the Medical, Surgical and Orthopedic Services of the Infants' and Children's hospitals in the Amphitheater of the Children's Hospital.

*8 p. m. Lecture on alcoholism, Miss Mildred G. Gray, in the amphitheater of the Mallory Institute of Pathology, 784 Massachusetts Avenue, Boston.

Tuesday, May 4—

9 a. m. Massachusetts General Hospital. Thoracic clinic. Ether Dome.

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Diagnosis and Treatment of Certain Hip Conditions. Dr. John D. Adams.

11:30 a. m. Massachusetts General Hospital. Eye-Nerve Conference. Outpatient department.

*8:30 p. m. Boston Society of Anaesthetists. Hotel Kenmore, Boston.

Wednesday, May 5—

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Hospital case presentation. Dr. Robert W. Buck.

†12 m. Clinicopathological conference. Children's Hospital amphitheater.

2 p. m. Massachusetts General Hospital. Psychiatric clinic. Outpatient department.

4 p. m. - 5 p. m. Surgical pathological conference. Dr. Cutler and Dr. Wolbach, Peter Bent Brigham Hospital.

*4 p. m. George Washington Gay Lecture, Room 6, Harvard Medical School.

6:30 p. m. Massachusetts Society of Examining Physicians. Copley Plaza Hotel, Boston.

Thursday, May 6—

9 a. m. Massachusetts General Hospital, Circulatory clinic rounds.

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Some Considerations in the Diagnosis and Treatment of Syphilis. Dr. William A. Hinton.

11 a. m. Massachusetts General Hospital. Medical grand rounds. Ether Dome.

12 m. Massachusetts General Hospital. Clinicopathological conference.

*5 p. m. Faulkner Hospital clinical meeting.

Friday, May 7—

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Hospital Social Service; Its Origin and Development. Dr. Richard C. Cabot.

11 a. m. Massachusetts General Hospital. Fracture rounds.

*8:15 p. m. Boston Society for the Advancement of Gastroenterology. Evans Memorial, East Concord Street, Boston.

Saturday, May 8—

*9 a. m. - 10 a. m. Boston Dispensary, 25 Bennet Street, Boston. Hospital case presentation. Dr. Robert W. Buck.

*10 a. m. - 12 m. Staff rounds at the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.
†Open to Fellows of the Massachusetts Medical Society.

April 29—Medical clinic at the Peter Bent Brigham Hospital, 3:30 p. m.

April 30—Henry Jackson Lecture, 4:45 p. m. Boston Medical Library, 8 Fenway.

April 30—Boston Pathological Society, 8 p. m., Tufts College Medical School.

April 30—Staff of the Massachusetts Memorial Hospitals, 8:15 p. m., 78 East Concord Street, Boston.

May 1-29—Boston Dispensary, Medical Conference Program. Page 770.

May 4—Boston Society of Anaesthetists. Page 770.

May 5—Massachusetts Society of Examining Physicians. Page 769.

May 5—George Washington Gay Lecture. Page 633, issue of April 8.

May 5, 6, 7 and 8—American Association on Mental Deficiency. Page 679, issue of April 15.

May 6—Faulkner Hospital Clinical Meeting. Page 769.

May 7—Boston Society for the Advancement of Gastroenterology. Page 678, issue of April 15.

May 10—New England Heart Association. Page 769.

May 12—National Hospital Day

May 13—Pentucket Association of Physicians. Hotel Bartlett, 95 Main Street, Haverhill, at 8:30 p. m.

June 7—American Medical Golfers Play in Atlantic City. Page 582, issue of April 1.

June 7 and 8—American Heart Association. Page 769.

June 7-11—American Medical Association. Atlantic City. Page 709, issue of April 22.

June 8—The American Neisserian Medical Society. Page 489, issue of March 18.

June 8 and 9—American Board of Obstetrics and Gynecology. Page 78, issue of January 14.

June 11-18—Catholic Hospital Association. Page 488, issue of March 18.

July 6-11—Fifth International Congress of Hospitals. Page 37, issue of January 7.

September 13-17—Fifth International Congress of Radiology. Page 709, issue of April 22.

October 5-8—American Public Health Association meeting. New York City.

October 9—American Board of Ophthalmology, Chicago. Page 722, issue of April 22.

October 19, 20, 21—Academy of Physical Medicine. Page 723, issue of April 22.

October 25-29—American College of Surgeons. Chicago, Illinois.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH DISTRICT MEDICAL SOCIETY

May 12—Annual meeting. Salem Country Club. Speaker: Dr. P. P. Johnson of Beverly. Subject: A Trip to the Bahamas and Guatemala. (Illustrated.)

R. E. STONE, M.D., Secretary.
74 Lothrop Street, Beverly.

FRANKLIN DISTRICT MEDICAL SOCIETY

Will meet at the Weldon in Greenfield at 11 a. m. the second Tuesday of May.

CHARLES MOLINE, M.D., Secretary.
Sunderland.

HAMPDEN DISTRICT MEDICAL SOCIETY

May 6—Censors' meeting. 20 Maple Street, Springfield. 4 p. m.

MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

May 12—Bear Hill Golf Club, Stoneham.

KENNETH L. MACLACHLAN, M.D., Secretary.
1 Bellevue Avenue, Melrose.

NORFOLK DISTRICT MEDICAL SOCIETY

May—Annual meeting.
May 6—Censors' meeting.

FRANK S. CRUICKSHANK, M.D., Secretary.
1247 Beacon Street, Brookline.

PLYMOUTH DISTRICT MEDICAL SOCIETY

May 20—11 a. m. Lakeville State Sanatorium.

FRED F. WEINER, M.D., Secretary.
231 Main Street, Brockton.

WORCESTER DISTRICT MEDICAL SOCIETY

May 6—At 4:30 in the rooms of the Worcester Medical Library, Inc., at 34 Elm Street, Worcester, will be held the spring meeting of the Board of Censors.

Wednesday Afternoon and Evening, May 12—Annual meeting.

ERWIN C. MILLER, M.D., Secretary.
27 Elm Street, Worcester.

BOOK REVIEWS

Juvenile Paresis. William C. Menninger. The Menninger Clinic Monograph Series No. 1. 199 pp. Baltimore: The Williams & Wilkins Company. $3.00.

Menninger's large series of forty-three personally studied cases of juvenile paresis have been the subject of twelve papers in scientific journals in the last two years. These reports, with additions, are now conveniently published in book form. The disease is rare, and only one previous monograph has been written upon it. Menninger's volume is therefore welcome. He not only reports his own cases in some detail but reviews the large periodical literature, which he has carefully compiled in a bibliography of over 500 references. The disease, usually associated with feeble-mindedness, runs a uniform course, with characteristic physical, neurologic and mental changes. Convulsions are common as an early symptom. Remissions are rare, and the outcome is nearly always death after four or five years. The diagnosis, prior to the serologic tests, was often difficult; with them, certainty is soon reached. Very occasionally, Menninger reports, the spinal fluid Wassermann test is negative. Treatment is extremely disappointing. Some patients, receiving antisyphilitic treatment from birth, have steadily progressed to a paretic death. Seven of Menninger's own cases, out of forty-three, showed some improvement. Treatment must be intensive, over a long period of time, without a rest period. A final chapter of this book deals with the pathology of the disease. Although the author has made some investigations by psychoanalysis, he, thoughtfully, leaves this subject out of his chapter on treatment. For this, as well as for his fine book, he deserves praise.

An Introduction to General Practice. E. Kaye Le Fleming. 150 pp. Baltimore: William Wood & Company, 1936. $2.00.

This is a very interesting, well-written book, in which the author earnestly, intelligently and convincingly advocates the thorough preparation of the medical student for his work as a general practitioner and, later, for keeping fully abreast of the advances in medical science and the rapid progress of the arts of healing and preventing disease.

Evidently the author has written especially to the recently graduated student who has completed his hospital internship and finds himself face to face with the difficult task of selecting a place to practice and of settling down to earn a living and establish himself in practice. He outlines many of the problems and difficulties which the young practitioner has to meet and overcome and gives sound advice as to how best to meet and manage them.

He devotes special attention to the British National Health Insurance Act of 1911, points out its beneficial and successful influences, and refers to the facts that upwards of 19,000,000 people have joined in the scheme and become insured and that more than 19,000 doctors are listed as participators in the work of caring for the insured.

The book is naturally and definitely written from the British viewpoint and for the guidance of British practitioners; but it contains much advice that might profitably be taken to heart by those who are newcomers into the medical profession here in America.

A Manual of Pharmacology. Walter E. Dixon. Revised by W. A. M. Smart. Eighth Edition. 483 pp. Baltimore: William Wood & Company. $6.50.

This book is a brief text with all the disadvantages of such a treatment of this subject. Such a volume is necessarily of the quiz-compend type, and the pharmacology it offers is that of a statement of what drugs do, rather than a detailed discussion of the mechanism of drug action. Much of the therapeutic procedure recommended is not explained from the pharmacologic point of view. Large numbers of preparations and mixtures are listed similar to those found in our "National Formulary." The merits and demerits of this rather bewildering array are not discussed. On the other hand, the organic chemistry of drugs is treated in detail far exceeding that found in any other English text. It may be questioned whether this phase of the subject should occupy so much space in a text of this size. However, this chemical emphasis makes the book a convenient reference work for those concerned with the structure of our common drugs.

Cystoscopy and Urography. James B. Macalpine. Second Edition. 478 pp. Baltimore: William Wood & Company. $9.00.

This book is "the last word" on cystoscopy. It is well written, and the facts are presented in a clear-cut fashion. This edition differs from the first in that new chapters have been added. These include familiar subjects, such as pelvic resorption, fistula of the bladder, pyeloscopy, congenital abnormalities of the kidney and ureter, funnel-neck deformity of the bladder and excretion urography. Many of the other chapters have been completely revised, and others have undergone slight revision. New illustrations have been generously added.

The reviewer is impressed with the great pains the author has taken to make this book a complete work on cystoscopy. There is no American equivalent.

The book is highly recommended to all urologists.

Bailey's Text-Book of Histology (Elwyn and Strong). Revised and Rewritten by Philip E. Smith. 773 pp. Ninth Edition. Baltimore: William Wood & Company. $6.00.

This textbook of histology, as stated in the preface, is designed primarily for the use of students rather than teachers and research workers. In keeping with this, it presents a clear and simple picture rather than a detailed discussion of controversial points. In this ninth edition, chapters I, VI, VII and XX have been rewritten. These deal respectively with the cell, the blood and lymph, the muscle and the organs of special senses. The arrangement and presentation are excellent throughout and, in spite of the number of revisers, the result is unified and readable. It has numerous, and for the most part excellent, illustrations with diagrams to correlate the gross appearances with the histologic findings. The physiologic changes found in the female reproductive system are well discussed.

No great space is devoted to the historical aspects of the subject. The embryology is brief but probably adequate. No bibliography is given. As a textbook for students, it is up-to-date and valuable. It is probably not elaborate enough to serve as a reference book for more advanced students.

The Eye and Its Diseases. By 82 International Authorities. Edited by Conrad Berens. 1254 pp. Philadelphia and London: W. B. Saunders Company. $12.00.

This book presents the essentials of ophthalmology in a concise form particularly suited to the needs of the general practitioner and medical student. More advanced students of ophthalmology will find a great deal of value in the text itself, and the references to the more important works in the literature offer a good starting point for further study.

It brings us up-to-date in our study of a rapidly changing specialty. The field of ophthalmology has become so broad that no one man can be considered an authority on all its phases. This book has particular value in that each contributor, by virtue of special interest or long experience, is especially well versed in his subject. It is a valuable contribution to the literature of ophthalmology.